

Poxvirus CORC: Mpox R&D Roadmap

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Poxvirus CORC: Mpox R&D roadmap

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Executive summary

Symptoms of mpox, caused by infection with monkeypox virus (**MPXV**), can include fever, painful skin lesions and potentially ocular and other complications. Two strains (**'clades'**) of MPXV have been identified – **clade I and clade II** – as well as subclades (**Ia, Ib, IIa and IIb)**, which differ in their epidemiology, pathogenicity and pathways of transmission. MPXV has been detected in multiple wild mammals, with small African rodents considered the most plausible natural reservoir; non-human primates are thought to be incidental spillover hosts.

Human MPXV infections in Africa were first detected in the 1970s. Since then, mpox cases have been primarily confined to African countries, following zoonotic spillover events and with limited human-to-human transmission, until a major global outbreak of clade IIb MPXV in 2022–23 and a clade I outbreak mainly affecting Africa in 2023–25. Although no longer considered a formal public health emergency, mpox cases continue to occur in multiple countries and the potential for wider epidemics remains.

MPXV is related to variola virus, the cause of smallpox, and vaccines developed for smallpox show efficacy against MPXV. Such vaccines have been deployed to control mpox outbreaks, particularly **MVA-BN** and **LC16m8**. There are no licensed therapeutics specifically developed for mpox and licensed smallpox treatments have shown minimal benefit in recent clinical trials.

The Mpox R&D Roadmap has been developed through a consultative community-wide effort coordinated by the **Poxvirus Collaborative Open Research Consortium (CORC)**, led by Institut National de Research Biomédicale, DRC (INRB) and Wits RHI, South Africa. It has taken a holistic approach, rooted in the overarching need to **minimise the public health impact of MPXV**. As well as the development of medical countermeasures for mpox, it therefore also considers other key issues relating to mpox control, including surveillance (clinical and environmental), infection prevention and control, social and behavioural interventions, and access, implementation and acceptability of medical countermeasures.

Mpox medical countermeasures: High-level overview of current status and priority needs

MCM type	Current status of field	Key needs
Diagnostics	• Multiple products available addressing a variety of diagnostic use cases. • No point-of-care diagnostic is in widespread routine use. • Non-standardised assays and evaluation methods make comparisons difficult.	• Rapid, reliable, easy-to-use and affordable point-of-care diagnostic.
Vaccines	• Safe and efficacious repurposed smallpox vaccines are available. • Pipeline reasonably well stocked.	• **Existing vaccines**: Closing remaining evidence gaps (e.g. duration of protection, use in special populations, population impact). • **New vaccines**: (1) additional products to strengthen market health/availability; (2) products with enhanced characteristics.
Therapeutics	• No effective antivirals available. • Antiviral pipeline poorly stocked. • Multiple antivirals and monoclonal antibodies in preclinical development.	• Safe, effective and affordable antivirals for treatment and post-exposure prophylaxis.

To facilitate development of the roadmap, six major areas were identified – epidemiology, host–pathogen interactions, therapeutics, vaccines, clinical care, and social and behavioural research – with the first area divided into three subsections (natural hosts and ecology, clinical epidemiology, and diagnostics). In each area, international writing groups have identified a set of high-level **knowledge gaps/research questions**, plus detailed technical questions, alongside **'enablers'** that could advance the field more generally.

Primary knowledge gaps:

1a: Ecology, natural hosts and zoonotic transmission

Key objective: To understand transmission of MPXV in the natural environment and spillover into humans

- **Natural host(s):** What are the natural hosts of MPXV?
- **Natural history:** What are the main transmission pathways between natural hosts?
- **Zoonosis:** What are the key risk factors for zoonotic transmission to humans?

1b: Mpox epidemiology in human populations

Key objective: To understand mpox disease burden, drivers of virus transmission, and viral evolution

- **Disease burden:** What is the true mpox disease burden and how is it distributed?
- **Transmission dynamics:** What are the key drivers of sustained human-to-human transmission in different clinical and non-clinical settings?
- **Viral evolution and adaptation:** How is MPXV evolving in human populations?
- **Functional consequences**: What are the implications of MPXV evolution?
- **Data for action**: How can epidemiological data best be delivered to policymakers to inform disease control and decision-making?

1c: Diagnostics

Key objective: To promote the development, evaluation and use of diagnostic tools to support clinical care and surveillance

- **Diagnostic design and target selection:** How can the design of new mpox antigen and molecular diagnostics be optimised according to different use cases?
- **Evaluation:** How can standardised specimen collection and evaluation methods be developed to deliver comparable and reliable data on test performance?
- **Deployment:** How can diagnostic tools best be deployed in clinical care and surveillance?

2: Host–pathogen interactions

Key objective: To understand MPXV biology, host responses and disease mechanisms

- **Host factors and immunity:** What genetic influences and immune mechanisms determine protection against MPXV infection and disease severity?
- **Viral evolution, clades and pathogenesis:** What are the evolutionary mechanisms driving MPXV adaptation and genetic determinants of clade-specific pathogenesis?
- **Cell and tissue biology of infection:** What are the mechanisms governing MPXV cell entry, cellular tropism, and dissemination?
- **Experimental model systems:** How can experimental systems be improved to better model MPXV infection and enhance translatability?

3: Clinical care and infection control

Key objective: *To optimise diagnosis, treatment and care of mpox patients (and associated complications) and prevent onward transmission of MPXV*

- **Natural history of infection**: How does the course of mpox disease vary by patient type?
- **Wound/lesion care**: What is the optimal approach to lesion care in different patient populations?
- **Special populations**: What are the optimal care pathways for special populations, including children, pregnant women and people living with HIV?
- **Secondary infections**: What is the best approach for preventing and treating secondary/co-infections?
- **Complications**: What are the best approaches for managing ocular and other complications of mpox?
- **Infection prevention and control**: What are the most effective ways to prevent mpox transmission in clinical and post-clinical settings?

4: Therapeutics

Key objective: To advance the development, clinical evaluation and implementation of mpox therapeutics

- **Existing therapeutics:** Is there a role for tecovirimat or other existing antivirals in mpox treatment?
- **Therapeutic development**: What other antivirals in development have potential as mpox treatments?
- **Host-directed therapies**: Do immune modulators or other host-directed therapies have potential as mpox treatments?
- **Biologics:** What monoclonal antibodies or other biologics in development have potential as mpox treatments?
- **Mpox complications:** Do existing or developmental therapeutics have potential in treatment of ocular or other mpox complications?

5: Vaccines

Key objective: To optimise the use of existing vaccines and accelerate the development and implementation of new products

- **Protective immunity:** What host responses confer protective immunity and which can be used as correlates of protection?
- **Optimising protection**: How well do existing vaccines protect different populations and what are the requirements for next-generation products?
- **Population benefits of vaccination:** What does real-world evidence reveal about the effectiveness, safety, durability of protection and population-level impact of currently used vaccines?
- **Outbreak control**: What impact do vaccines have on MPXV transmission and outbreak dynamics?
- **Programme design and implementation**: What delivery strategies and programme approaches will maximise mpox vaccination uptake, equity, timeliness and impact in affected communities?

6: Social and behavioural science and implementation research

Key objective: To understand the knowledge, attitudes and practices of key stakeholders (including community members and policymakers) to facilitate research and implementation of medical countermeasures and other strategies to minimise the public health burden of mpox

- **Community trust:** What are the best ways to build sustainable trust and leverage community-led mobilisation to improve the uptake of medical countermeasures and behavioural changes across diverse populations?
- **Stigma, discrimination and inclusive language:** How do stigma, discrimination and communication practices shape access to care, participation in research, and uptake of medical countermeasures during mpox outbreaks, and what strategies can mitigate these barriers across contexts?
- **Care seeking and service pathways:** How do social, structural and economic factors influence the journey from symptom onset to recovery, and how can pathways be optimised to ensure equitable access to care?

- **Vaccination confidence, behaviour and delivery:** What behavioural, social and structural factors influence uptake of mpox vaccines, and how can vaccination strategies be optimised to improve uptake across diverse contexts?
- **Implementation research for systems integration:** How can health systems and surveillance infrastructures be optimised and integrated to ensure the equitable, timely and scalable delivery and evaluation of mpox medical countermeasures across diverse and resource-constrained environments?
- **Engagement with R&D:** How can social, behavioural and participatory research/co-production be integrated throughout the R&D lifecycle to build community trust, ensure ethical trial conduct, and maximise the social acceptability of mpox interventions?

Enablers:

Writing groups identified multiple enablers within their focus areas. These have been consolidated into four general categories. Where indicated with an asterisk, there are opportunities for an integrated approach to be taken across WHO priority pathogen families.

1. Surveillance and outbreak response accelerators

- **Surveillance systems**: Integrated clinical, environmental, One Health and community-based surveillance, with genomic capabilities*:
    - *Required to track zoonotic spillovers, changing epidemiology and viral evolution, and to underpin outbreak responses and disease control interventions.*
    - *Dependent on appropriate diagnostic tools (including genomics technology), laboratory capacity, data management systems, data analytics tools, human capacity development.*
    - *Important to include vaccination status in surveillance data to generate insights into population impacts of vaccination.*

- **Outbreak response:** Integration of data collection and analysis into outbreak response planning and implementation*
    - *Ensures (1) an evidence-based response to outbreaks and (2) collection of new data to optimise current and future responses.*
    - *Requires integration of surveillance data analysis into national public health systems with user-friendly tools (e.g. digital dashboards) to guide policymaking, disease control and outbreak response.*
    - *Would benefit from strengthening of modelling capacity to inform policymaking.*
    - *Requires consideration of mpox-specific factors, including potential involvement of special populations and impact of stigmatisation.*
    - *Requires input from social and behavioural science expertise to shape both response strategies and integral research activities.*
    - *Provides opportunities for implementation/operational research and incorporation of learning into future outbreak responses.*

2. MCM development accelerators

- **Updated target product profiles (TPPs):** Review and revision (if necessary) of TPPs to guide intervention development.
- **Biobanks/repositories:** Sample collections and data repositories maintained as a public good, with equitable access to all legitimate researchers.

    - *May be a combination of centralised infrastructure and a federated network with common, streamlined access protocols.*
- **Standardised materials/assays/endpoints/evaluations:** Standardised and validated methods/tools to ensure quality, consistency and data compatibility to inform decision-making.
- **Global/regional nodes:** Global or regional centres providing guidance and practical support for diagnostic evaluation studies.
- **Animal models:** Standardised and optimised animal models to ensure data compatibility and to de-risk intervention development (greater fidelity).
- **Research partnerships:** Strong, equitable research partnerships along the intervention development pathway.
- **Addressing biosafety barriers:** Ensuring widespread access to biosecure and accredited laboratory facilities suitable for MPXV research and developing methods that facilitate research outside BSL-2/3 facilities.

3. Clinical study preparedness

- **Clinical trial capacity/networks/platforms***: Sites in regions affected by mpox with the capacity to rapidly launch clinical studies during outbreaks.
    - *Given ongoing transmission of MPXV in many settings, some research studies could be carried out even in the absence of a large-scale outbreak.*
    - *Trial networks/platforms could accelerate intervention evaluation by facilitating adaptive trials.*
- **Pre-reviewed trial protocols*:** Standardised protocols developed and reviewed in advance of outbreaks.
    - *Need to incorporate social and behavioural data collection.*
- **Harmonised and speedy regulatory systems***: Rapid regulatory and ethics review mechanisms to review 'core' protocols in advance of an outbreak and finalised protocols, to ensure rapid launch of studies.
    - *May require strengthening of national regulatory authorities and enhanced preparedness to support pre-approval processes.*
    - *Learn from successful applications in other fields.*

4. Access/implementation accelerators

- **Strong and ongoing community engagement/involvement***: Trust building to ensure strong support for and participation in research and take up of new interventions.
- **Research/policymaker collaborations***: Strengthening of academic–policymaker partnerships to promote evidence-based policymaking and policy-relevant research.
- **Regulatory harmonisation***: Alignment and streamlining of regulatory processes to accelerate approvals and introductions, and leveraging of reliance mechanisms.
- **Special populations*:** Strategies to ensure the rapid collection of data to support use of interventions in special populations (e.g. children, pregnant women, people living with HIV).
- **Sustainable and equitable access:** Strategies for financing, economic analyses, pooled procurement and incentivisation to ensure the availability of MCMs in high-burden countries and during outbreaks.
- **Regional technical transfer/manufacturing***: Integration of mpox intervention development into wider strategies to ensure regional health security.

These enablers highlight two key aspects of mpox R&D:

- **Preparedness:** An integrated set of activities is required to ensure that mpox outbreaks are swiftly detected and brought under control. This will require ongoing commitments to strengthen surveillance, develop new medical countermeasures (diagnostics, vaccines and therapeutics), strengthen capacity to

systematically evaluate these tools before and during outbreaks, harmonise and streamline regulatory processes, and build and sustain public trust.

- **Data for action:** Research, routine programmatic activities, plus implementation research combining the two, all generate data with the potential to inform outbreak prevention and control. Data generation should be strongly focused on policymaker needs with data delivered in ways that enable policymakers and others to act upon the latest evidence.

Moving forward on many of these enablers will require collaboration between multiple stakeholders, including the research community, global agencies, funders and countries. This consolidated list of priorities can provide a framework for further collaborative research efforts to better understand the threat posed by MPXV and how it can best be controlled.

Anticipated timelines

The following tables highlight immediate priorities (2026–2028) and anticipated follow-on work and longer-term priorities within each thematic area.

1a. Ecology ***Key objective: To understand transmission of MPXV in the natural environment and spillover into humans***	
2026–28	2028–
Natural hosts: Clarify nature of MPXV hosts for all clades and different ecological habitats	**Prevention**: Design and evaluate zoonotic prevention strategies informed by local contexts
Transmission pathways: Clarify routes of transmission between natural hosts and role of arthropod or other vectors	**Long-term trends**: Explore potential impact of climate change and other socio-environmental factors on MPXV
Risk factors: Identify main biological, socio-behavioural and environmental risk factors for zoonotic transmission	**Modelling**: Develop and deploy predictive models of MPXV zoonotic transmission to target prevention efforts
Surveillance: Establish frameworks for integrated One Health surveillance and promote national adoption	**Surveillance:** Strengthen One Health surveillance systems and outbreak prevention/response mechanisms
Sample and data access: Develop strategies to ensure equitable access to surveillance data and samples	**Access:** Create repositories and frameworks to optimise access to genomic resources and use of biological samples

1b. Epidemiology ***Key objective: To understand mpox disease burden, drivers of virus transmission, and viral evolution***	
2026–28	2028–
Disease burden: Clarify disease burden, by clade, geography and population	**Outbreak response**: Ensure national surveillance systems effectively detect nascent outbreaks
Transmission dynamics: Improve understanding of transmission pathways for different MPXV clades	**Surveillance**: Ensure strong integration of data from multiple sources (genomic, wastewater, animals, clinical)
Viral evolution: Map MPXV genetic variation and evolution, within patients and populations	**Functional assessments**: Ensure close links between surveillance and labs for functional characterisation
Surveillance: Strengthen national surveillance systems and data use to inform decision-making	**Data use:** Ensure evidence is delivered to policymakers in actionable formats
Laboratory capacity: Standardise assays and strengthen local laboratory capacities in affected countries	

1c. Diagnostics *Key objective: To promote the development and use of diagnostic tools to support clinical care and surveillance*	
2026–28	2028–
TPPs: Revise TPPs for key use cases (community-based RDTs, POC/near-POC molecular, laboratory confirmation)	**Surveillance**: Promote integration of diagnostics into national surveillance activities and use to inform action
Standardisation: Establish standardised approaches for sample collection and device evaluation	**Approvals:** Harmonise and streamline regulatory pathways and introduce a rationalised emergency use pathway
EQA: Develop standardised and validated assays and introduce a regional/global EQA programme	**EQA**: Ensure at least two regional/global EQA programme proficiency rounds are run each year
Landscaping: Document current national diagnostic capacity and practice and develop models of deployment	**Support hub**: Launch support hub and regional/subregional nodes, including reference material repositories
Support hub: Develop coordinating structures and scope of regional/subregional development-support nodes	**Affordability:** Explore pooled procurement and market-shaping mechanisms to ensure affordability
Data/specimen access: Enable rapid, equitable specimen sharing, with broad consent for future diagnostic R&D	**Access**: Develop regional strategy for ensuring access to required diagnostics

2. Host–pathogen interactions *Key objective: To understand MPXV biology, host responses and disease mechanisms*	
2026–28	2028–
Immunity: Clarify key elements of protective immunity at different exposure sites and immune evasion mechanisms	**Translation**: Promote use of new understanding to advance therapeutic development
Genetic variation: Understand functional consequences and clinical implications of MPXV genetic variation	**Model systems**: Promote use of standardised models and explore alternatives (e.g. organoids, in silico models)
Cell and tissue biology: Develop more detailed mechanistic understanding of MPXV life cycle	**Assays/reagents**: Promote use of standardised assays, with periodic updating based on MPXV evolution
Model systems: Refine and standardise animal models of MPXV infection, for key sites of exposure	
Assays/reagents: Develop standardised assays and reagents to advance translational research	

3. Clinical care *Key objective: To optimise diagnosis, treatment and care of mpox patients (and associated complications) and prevent onward transmission of MPXV*	
2026–28	2028–
Diagnosis/triage: Identify optimal pathway for initial assessment of potential mpox cases in different settings	**Diagnosis/triage:** Develop/update guidelines on initial assessment in different settings
Wound/lesion care: Identify most effective care strategies for different presentations and populations	**Wound/lesion care**: Develop/update guidelines on care in different settings and for different populations
Complications: Clarify key complications and identify optimal care in different patient groups	**Complications**: Develop/update guidelines on care for ocular and other complications
IPC: Clarify key transmission routes in clinical and non-clinical settings	**IPC**: Develop and evaluate interventions to reduce MPXV transmission in clinical and non-clinical settings
Outcome measures: Agree standardised outcome measures	**Capacity building**: Strengthen capacity for clinical studies in endemic settings

4. Therapeutics

Key objective: To advance the development, clinical evaluation and implementation of mpox therapeutics

2026–28	2028–
Existing therapeutics: Establish consensus on clinical utility of existing therapeutics	**Technological innovations**: Ensure emerging technological innovations are applied to mpox therapeutic development
TPP/TCP: Update existing TPP and develop a target compound profile (TCP) for mpox therapeutics	**Trial platforms**: Establish clinical trial networks in affected countries to evaluate candidate therapeutics
Standardisation: Develop standardised outcome measures, assays and reference materials	**Regulatory processes**: Harmonise/streamline regulatory processes to ensure timely access to new therapies
Animal models: Review translational utility of existing animal models	**Manufacturing and access**: Explore opportunities for tech transfer and development of regional manufacturing
Capacity building: Strengthen capacity for all phases of therapeutic development and evaluation in affected regions	

5. Vaccines

Key objective: To optimise the use of existing vaccines and accelerate the development and implementation of new products

2026–28	2028–
Protective immunity: Advance correlates of protection identification and validation	**Refine deployment strategies**: Use new evidence to shape programmatic use of vaccines
Population benefits: Clarify effectiveness and durability of protection provided by existing vaccines	**New vaccine testing**: Test candidate vaccines in affected settings, potentially via platform trials
Outbreak control: Determine contribution made by existing vaccines to outbreak control	**Use of COPs**: Apply COPs in vaccine development and (potentially) licensing (e.g. immunobridging)
Programme design: Identify optimal deployment strategies and optimise programmatic management	**Manufacturing**: Explore options for regional vaccine manufacturing
Capacity building: Strengthen capacity for clinical and laboratory vaccinology studies in endemic regions	
Vaccine development: Advance new vaccines to boost supply and address limitations of existing products	

6. Social and behavioural science

Key objective: To understand the knowledge, attitudes and practices of key stakeholders (including community members and policymakers) to facilitate research and implementation of medical countermeasures and other strategies to minimise the public health burden of mpox

2026–28	2028–
Care-seeking: Improve understanding of factors affecting use of services in different settings	**OBR:** Ensure SBS considerations are integrated into national/subnational outbreak responses
Vaccine confidence: Improve understanding of social and behavioural drivers of vaccine uptake in different settings	**Vaccines:** Develop and evaluate local interventions based on BeSD data to increase vaccine take up
R&D: Improve understanding of factors affecting willingness to participate in research studies	**R&D:** Ensure community perspective is embedded throughout all stages of MCM R&D
Implementation research: Leverage community-focused implementation research to enhance services and take up	**IR:** Strengthen programmatic capacity to apply implementation research to enhance care and OBR
Communities: Build frameworks/mechanisms to promote community involvement in R&D, service design and OBR	**Stigma**: Develop criteria for assessing stigma, explore its impact, and collate evidence on stigma mitigation/reduction

Introduction

Mpox is characterised by a variety of flu-like symptoms, a rash and painful skin lesions. It is spread by close person-to-person contact. Although often mild and self-limiting, mpox cases can be severe in vulnerable groups, particularly children and people living with uncontrolled HIV.

Mpox, a zoonotic viral disease, is caused by infections with *Orthopoxvirus monkeypox* (monkeypox virus, MPXV). MPXV was identified in monkeys in the 1950s, with the first human case detected in the Democratic Republic of the Congo (DRC) in 1970[1]. Two main strains or 'clades' of MPXV have been distinguished – clades I and II. Subtypes of these clades exist (clades Ia and Ib, IIa and IIb), with differing pathogenic potential.

MPXV is found in a variety of wild animals, with human infections traditionally occurring by zoonotic transmission. MPXV can also be spread from person-to-person following close contact, including sexual contact[2]. Transmission patterns vary for the different clades and sub-clades of MPXV.

Until the 2020s, human-to-human transmission was limited and mostly confined to countries in Africa. In 2022, global spread of **clade IIb MPXV**, driven mainly by sexual contact, led WHO to declare a Public Health Emergency of International Concern (PHEIC). This emergent virus was derived from a clade IIb variant that had been circulating for some time in Nigeria[3].

While this global PHEIC was lifted in 2023, an mpox **clade I outbreak** originating in the DRC led to declaration of a second PHEIC in 2024; it was also categorised as a Public Health Emergency of Continental Security (PHECS) by the Africa Centre for Disease Control and Prevention (Africa CDC). This outbreak was linked to the emergence of a novel clade I variant, **sub-clade Ib**[4]. The second PHEIC was closed in 2025 and the PHECS in early 2026.

In February 2026, WHO reported cases of **recombination between MPXV strains** (clade Ib and IIb) in India and the UK[5], highlighting the potential for viral evolution through 'genomic mixing' as well as clade-specific divergence. The two cases likely reflect infection with the same recombinant variant; no further cases have been detected. The patients infected did not experience abnormally severe symptoms.

[1] Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. Bull World Health Organ. 1972;46(5):593-7.

[2] Thornhill JP, Barkati S, Walmsley S et al. Monkeypox Virus Infection in Humans across 16 Countries - April-June 2022. N Engl J Med. 2022;387(8):679-691. doi: 10.1056/NEJMoa2207323.

[3] Gigante CM, Korber B, Seabolt MH et al. Multiple lineages of monkeypox virus detected in the United States, 2021-2022. Science. 2022;378(6619):560-565. doi: 10.1126/science.add4153.

[4] Vakaniaki EH, Kacita C, Kinganda-Lusamaki E et al. Sustained human outbreak of a new MPXV clade I lineage in eastern Democratic Republic of the Congo. Nat Med. 2024;30(10):2791-2795. doi: 10.1038/s41591-024-03130-3.

[5] https://www.who.int/emergencies/disease-outbreak-news/item/2026-DON595

***Table 1**: Comparison of MPXV clades and sub-clades*

Clade	Geographic origin	Burden	Severity*	Transmission	Affected populations
Ia	Central Africa (Congo basin)	Mostly localised rural outbreaks	More severe (CFR 5–10%)	High transmissibility/ virulence	All ages, including children
Ib		2024–25 PHEIC/PHECS	Less severe (CFR 0.3–1.4%)	Human-to-human	Mostly GBMSM in high-income settings; more broadly in Africa
IIa	West Africa	Mostly localised rural outbreaks	Less severe (CFR ≤3%)	Mostly zoonotic	Mostly those in contact with natural hosts
IIb		2022–23 PHEIC	Less severe (CFR ≤3%)	Zoonotic, enhanced human-to-human spread	Mostly GBMSM

CFR: Case fatality rate; GBMSM: gay and bisexual men who have sex with men.
*Published CFR figures vary significantly and are dependent on setting, quality of supportive care and population affected.

MPXV virology: MPXV is a complex **double-stranded DNA virus**, with around 200 genes. It can infect multiple cell types, including epithelial, endothelial and various immune cells, through attachment to cell-surface mucopolysaccharides (**glycosaminoglycans, GAGs**). Following infection, the virus replicates in the cell cytoplasm, hijacking the secretory mechanisms of host cells to traffic infectious viral particles to the cell surface. MPXV also deploys multiple methods of **immune evasion**, interfering with various innate and cellular immune mechanisms to delay viral clearance[6].

Current epidemiology and burden: In the first half of 2026, MPXV continued to circulate in multiple countries, with introductions occurring in previously unaffected territories following importation. Clades Ib and IIb continue to circulate in human populations, particularly in Africa, which accounts for around two-thirds of cases. New zoonotic infections continue to occur in areas where MPXV is present in natural hosts.

Diagnosis: Clinical diagnosis of mpox can be challenging, as symptoms are shared with other orthopoxvirus infections such as chickenpox (varicella) and some sexually transmitted infections. Molecular methods such as PCR can detect the presence of MPXV and identify which clade an isolate belongs to. Genomic sequencing can provide full genetic characterisation, helping to track viral evolution (and identify cases of recombination).

Prevention: Smallpox/orthopoxvirus vaccines are expected to confer cross-protection against mpox. Those used most extensively to date include **MVA-BN** (non-replicating) and **LC16m8** (live attenuated). MVA-BN has received widespread approvals for use in adults and was WHO-prequalified in 2024. LC16m8 is licensed in Japan for use in all age groups, including children, and received WHO emergency use listing in 2024. Real-world evidence on clinical effectiveness is strongest for MVA-BN against clade IIb, but more limited for LC16m8, clade I virus and special populations. Duration of protection and impacts on transmission are also uncertain. WHO's Strategic Advisory Group of Experts on Immunisation (SAGE) has issued various guidance relating to the use of these vaccines[7].

Treatment: No specific therapeutics exist for mpox. Therapeutics originally developed for smallpox, including **tecovirimat**, have been found to provide limited clinical benefits and some, such as **cidofovir/brincidovir**, are

[6] Full F, Port JR, Bojkova D. Monkeypox virus: the complexities of a resurgent threat. Am J Physiol Cell Physiol. 2026 Apr 1;330(4):C891-C908. doi: 10.1152/ajpcell.00575.2025.

[7] https://www.technet-21.org/en/resources/presentation/summary-of-who-sage-recommendations-for-mpox-vaccines-including-considerations-for-off-label-use

associated with significant toxicity concerns. Several therapeutics are in clinical and pre-clinical development, including both narrow-spectrum (orthopoxvirus-specific) and broad-spectrum agents (with wider antiviral activity).

Clinical care is therefore mostly supportive. Specific treatments may be used for complications associated with MPXV infection, such as eye conditions.

Cross-cutting issues

One Health: New MPXV infections (mostly clades Ia and IIa) continue to be detected following zoonotic transmission. Circulation within animal populations and the potential for **'reverse zoonosis'** – transmission from humans back to animals – could raise the risk of MPXV evolution into more human-transmissible or pathogenic variants. Mpox control therefore needs to be considered within a One Health framework that recognises the importance of human–animal contact and environmental disruption to mpox transmission.

Special populations: Certain populations are at particular risk of poor outcomes following MPXV infection. These include **pregnant women**, who are more likely to experience severe disease as well as adverse birth outcomes[8], and children, who may be more susceptible to infection and experience worse outcomes[9]. MPXV can also have severe consequences for people living with uncontrolled HIV infection[10]. Infection of **immunocompromised hosts** can provide an opportunity for an extended period of unchecked replication, leading to viral evolution and promoting the emergence of new variants. R&D strategies for mpox medical countermeasures need to consider these populations as a high priority.

Stigma: Mpox is associated with considerable **stigma and discrimination**, in part because of its association with gay, bisexual and other men who have sex with men (GBMSM) populations during the global clade IIb outbreak. This can have significant social consequences for those affected by mpox, and can drive behaviours that are counter-productive to effective mpox control, such as delayed treatment-seeking[11]. Stigma might also affect the willingness to take part in clinical research, including trials of mpox medical countermeasures.

Research into mpox medical countermeasures and their deployment therefore needs to incorporate **social and behavioural** research into the knowledge, attitudes and practices of key stakeholder groups, including community members.

Access and accessibility: The burden of mpox is currently greatest in sub-Saharan Africa, which therefore has the greatest need for medical countermeasures. It is essential that intervention development for mpox considers access issues at an early stage, to ensure that new products reach settings of greatest public health need as rapidly as possible.

In addition, product development needs to focus on **implementation** in resource-poor settings. Product design therefore needs to reflect the realities of under-resourced health systems and challenging environmental conditions. Efficacy and performance also need to be demonstrated in the populations most affected.

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[8] Vakaniaki EH, Barhishindi I, Mubiala A et al. Maternal and neonatal outcomes after infection with monkeypox virus clade I during pregnancy in DR Congo: a pooled, prospective cohort study. Lancet. 2026;407(10525):256-266. doi: 10.1016/S0140-6736(25)02309-8.

[9] Dsouza VS, Kurian JR, Brand A. Epidemiology and clinical manifestation of mpox in children: Systematic review and meta-analysis. Glob Public Health. 2026;21(1):2648960. doi: 10.1080/17441692.2026.2648960.

[10] Mitjà O, Alemany A, Marks M et al. Mpox in people with advanced HIV infection: a global case series. Lancet. 2023;401(10380):939-949. doi: 10.1016/S0140-6736(23)00273-8.

[11] Foláyan MO. Mpox, stigma and the Public Health Emergency of Continental Security declaration: Addressing public health challenges in Africa. J Public Health Afr. 2024;15(1):757. doi: 10.4102/jphia.v15i1.757.

Integration: Many of the issues relating to mpox medical countermeasure development are also relevant to other outbreak-prone pathogens. Cross-family coordination across roadmaps will help to identify actions that deliver generic benefits, for example in areas such as surveillance and clinical trial capacity.

Purpose of this R&D Roadmap

This R&D Roadmap is intended to provide a consensus view of the key gaps in knowledge and other challenges affecting the development, evaluation and deployment of medical countermeasures against mpox. It provides a foundation for collaborative efforts to address these challenges and advance medical countermeasure development to prevent, curtail and minimise the population health impact of mpox outbreaks.

Once the R&D Roadmap is finalised, the CORC team will shift its focus to supporting community-wide efforts to address the knowledge gaps identified and accelerate medical countermeasure development. We will be developing plans for further engagement with the CORC community to better understand needs, barriers and opportunities, to identify how the CORC can best facilitate coordinated and collaborative approaches to advance mpox R&D and disease control.

Development of the R&D Roadmap

The Mpox R&D Roadmap was collaboratively developed through a global consultative process coordinated by the **Poxvirus Collaborative Open Research Consortium (CORC)**, led by Jean-Jacques Muyembe, Institut National de Research Biomédicale, DRC (INRB) and Helen Rees, Wits RHI, South Africa.

Six thematic areas were identified, with the first divided into three subthemes. Global writing groups were set up in each of these eight areas with leads from the DRC and South Africa. Each group developed a draft chapter of the R&D Roadmap, focusing on **knowledge gaps**/research questions and **'enablers'** – activities that could facilitate or accelerate mpox R&D and evidence-based medical countermeasure use.

Writing groups were encouraged to consider the types of study that would be needed to close knowledge gaps and to provide a broad assessment of the importance of each knowledge gap and enabler. This prioritisation is the consensus of each writing group but was not based on systematic criteria and should be taken only as a general indication of importance. Each chapter was reviewed by a small group of global technical specialists.

The chapters were combined into a single consolidated document and the draft Mpox R&D Roadmap was circulated to the CORC community for comment. A revised version was then shared globally by the WHO. This version of the Roadmap incorporates global feedback.

The Mpox R&D Roadmap is designed to provide a common framework to guide the work of researchers and other R&D stakeholders. Looking forward, the CORC is identifying how it can strengthen coordination, collaboration and cooperation across the poxvirus R&D community, and what activities it can undertake to facilitate and accelerate the development, evaluation and implementation of medical countermeasures, working closely with other stakeholders.

It is anticipated that progress in closing knowledge gaps and advancing R&D enablers will be reviewed in early 2028.

1.1 Natural hosts, ecology and zoonotic transmission

MPXV is thought to be maintained in nature through a **complex, multi-host reservoir system** rather than in a single definitive animal species. **Small mammals**, particularly African rodents such as rope squirrels (*Funisciurus* spp.), Gambian pouched rats (*Cricetomys* spp.), dormice (*Graphiurus* spp.) and striped mice (*Hybomys* spp.), are considered the most plausible reservoir or amplifying hosts, while **non-human primates** are regarded as incidental spillover hosts. Spatial overlap analyses of ecological niches for African mammal species and human cases consistently identified **squirrels** (particularly rope squirrels) as the most likely source of human infections[12]. However, there is little direct evidence of transmission from these animals to humans.

A recent outbreak of MPXV in wild sooty mangabeys (*Cercocebus atys*) in Côte d'Ivoire was shown to be linked to transmission from the fire-footed rope squirrel (*Funisciurus pyrropus*), on which monkeys feed[13]. This suggests **wildlife hunting and consumption** as a potential transmission route to primates, including humans (consistent with epidemiological studies in the 1980s in the DRC on risk factors for transmission). Field studies and experimental infections suggest that some rodent species can sustain prolonged infection and shed high viral loads via saliva, faeces, urine and respiratory secretions, facilitating environmental contamination and zoonotic transmission.

Distinct **clade-specific host associations** have been observed. Clade I viruses are overwhelmingly sampled from humans, consistent with endemic circulation and repeated spillover in Central Africa, whereas clade IIa viruses are more frequently isolated from animals, suggesting differences in surveillance intensity, host susceptibility, or transmission efficiency. A US outbreak in 2003 of 72 cases, for example, was linked to MPXV transmission from imported African animals to prairie dogs followed by prairie dog to human infection[14].

Environmental and anthropogenic factors, such as climate change, deforestation, land-use change, wildlife trade, bushmeat consumption and expanding interactions at the human–animal and environment interface, are thought to increase spillover risk. **Socio-economic and cultural conditions,** including poverty, population growth, population movements between rural and urban areas, and displacement due to conflict, are likely also contributing to geographic spread by affecting human contact with animal hosts.

Transmission routes include direct contact with lesions, bodily fluids, respiratory secretions, contaminated fomites and, in zoonotic contexts, handling or consumption of infected animals. MPXV environmental stability further enables indirect transmission, with viral DNA detected in wastewater and other environmental samples, highlighting the potential utility of environmental surveillance as a population-level monitoring tool. **Reverse zoonosis**, including documented human-to-dog transmission[15], further complicates mpox ecology by raising the possibility of novel reservoir establishment outside Africa.

[12] Curaudeau M, Besombes C, Nakouné E et al. Identifying the most probable mammal reservoir hosts for monkeypox virus based on ecological niche comparisons. Viruses. 2023;15(3):727. doi: 10.3390/v15030727.

[13] Riutord-Fe C, Schlotterbeck J, Lagostina L et al. Transmission of MPXV from fire-footed rope squirrels to sooty mangabeys. Nature. 2026;651(8104):185-190. doi: 10.1038/s41586-025-10086-y.

[14] Ligon BL. Monkeypox: a review of the history and emergence in the Western hemisphere. Semin Pediatr Infect Dis. 2004;15(4):280-7. doi: 10.1053/j.spid.2004.09.001.

[15] Seang S, Burrel S, Todesco E et al. Evidence of human-to-dog transmission of monkeypox virus. Lancet. 2022;400(10353):658-659. doi: 10.1016/S0140-6736(22)01487-8.

Variation within the 200 kb MPXV genome contributes to differences in virulence, transmissibility and host adaptation between clades. Some clade IIb lineages exhibit mutational patterns consistent with sustained replication in humans[16]. Although clade I viruses have historically shown fewer such signatures, they have been detected in clade Ib isolates, indicating sustained human-to-human transmission[17]. Structural genomic variation can affect MPXV diagnostics, emphasising the need for continuous genomic surveillance, particularly in MPXV-endemic regions.

[16] Gigante CM, Korber B, Seabolt MH et al. Multiple lineages of monkeypox virus detected in the United States, 2021-2022. Science. 2022;378(6619):560-565. doi: 10.1126/science.add4153.

[17] Masirika LM, Udahemuka JC, Schuele L et al. Epidemiological and genomic evolution of the ongoing outbreak of clade Ib mpox virus in the eastern Democratic Republic of the Congo. Nat Med. 2025;31(5):1459-1463. doi: 10.1038/s41591-025-03582-1.

KNOWLEDGE GAPS:

Subtheme 1: Natural reservoir(s)			
What are the natural hosts of MPXV?			
Knowledge gaps	**Rationale**	**Importance**	**Approach**
Brief description of knowledge gap/research priority	*Statement of why this knowledge gap is important and how closing it would advance MCM development or implementation*	*Very high, high, medium or low*	*Types of study that could address knowledge gap*
Natural reservoir: What animal species function as long-term natural reservoirs of MPXV?	Spillovers from natural reservoirs remain an important source of human infection. It is important to understand if there is a single reservoir or multiple reservoirs and what species to target in prevention activities.	High	Targeted risk-based longitudinal ecological surveillance.
Geography: How do natural reservoirs vary across different geographic settings?	Key sources of human infection may vary between different geographic settings.	High	As above.
Clade specificity: Do different MPXV clades have different natural reservoirs?	MPXV clades may vary in their natural reservoirs, affecting human transmission risks.	High	As above.
New reservoirs: What is the potential for MPXV to become established in animal reservoirs in 'non-endemic' areas?	MPXV appears able to survive in a variety of host species. Due to international trade in exotic animals, it was briefly detected in prairie dogs in the USA. Theoretically, it could become established in new animal populations through this or other routes.	Medium	As above.

Subtheme 2: Mpox epidemiology in natural hosts			
What are the main transmission pathways between natural hosts?			
Knowledge gaps	**Rationale**	**Importance**	**Approach**

Virus circulation: Through which ecological transmission pathways is MPXV maintained and circulated among wildlife reservoirs and transmitted to other non-primary host species (e.g. primates)?	It is likely that there is more than one reservoir species. It is important to understand what species have the capacity to maintain and spread the virus and how intra-species and inter-species transmission occurs. This knowledge will also be important in establishing the MPXV mutation rate and in answering questions on natural selection.	High	Mix of bio-surveillance and application of genomics technology.
Rat hosts: What role do rats play in MPXV maintenance in natural environments?	Carriage by *Rattus* spp. could facilitate transmission within the natural environment and spillover to humans.	Very high	Mix of bio-surveillance and application of genomics technology.
Arthropod vectors: What is the role of arthropod vectors in MPXV transmission in natural reservoirs?	Arthropods could potentially transmit MPXV between hosts in the natural environment.	Medium	Arbovirology studies.
Environmental reservoirs: What is the role of environmental reservoirs in circulation of MPXV in the natural environment?	Persistence of MPXV in environmental reservoirs could contribute to transmission within natural host reservoir species (and present a risk for spillover).	High	Environmental water and soil sampling; application of genomics technology.
Biogeographic barriers: What are the biogeographic barriers that segregate the MPXV clades in natural environments?	The distribution of mpox clades differs based on geography, but it is not clear why certain clades are found in certain regions and not others, and what makes them persist in these regions. Biogeographic barriers such as rivers could play a role in shaping the presence of MPXV variants by preventing migration of natural reservoir species.	Very high	Landscape genetic studies. Phylogenetic and molecular clock analysis.
Reverse zoonosis: What is the role of spillback events in maintaining MPXV in natural reservoirs?	Understanding the dynamics of spillover and spillback events is important for	High	Systematic review/evidence synthesis, spatial ecological studies, seroprevalence studies.

	establishing control strategies. Little is currently known about spillback events.		
New reservoirs: What is the potential for MPXV to become established in new geographies?	MPXV could potentially be transmitted to squirrel species outside Africa or rodents in non-endemic settings (e.g. prairie dogs in the USA).	High	Experimental studies of MPXV infectivity and transmissibility in potential non-African host species.
Veterinary virology: How do viral persistence, shedding patterns and interspecies transmission operate within reservoir communities under natural ecological conditions in different settings?	Properties of the virus in natural hosts will affect the risk of zoonotic transmission.	Medium	Biological studies in natural hosts and environmental testing.
Genetic adaptation: What are the functional consequences of genomic diversity, gene duplications, and deletions for host adaptation?	Useful to understand the functional consequences of genomic changes, to predict host adaptation, assess the risk of sustained transmission in new populations or species, or anticipate evolutionary trajectories that could modify outbreak dynamics.	High	*See Human–Pathogen Interactions section.*

Subtheme 3: Risk factors for zoonotic transmission			
What are the key risk factors for zoonotic transmission?			
Knowledge Gaps	**Rationale**	**Importance**	**Approach**
Human–animal interactions: Which human–animal interaction patterns (e.g. hunting, wildlife trade, pet ownership, household exposure) most strongly increase the risk of zoonotic spillover and reverse zoonotic transmission of MPXV?	Identification of key human–animal interaction patterns will inform efforts to prevent and reduce outbreak occurrence by enabling One Health evidence-based interventions and preparedness. Drivers and interactions should be characterised in both endemic and non-endemic affected countries.	High	Analytical epidemiological studies case–control and cohort studies. Genomic surveillance and phylogenetic studies. Integrated One Health modelling studies.

Trends in risk-related activities: How are practices associated with increased risk changing over time?	Ecosystem disruption may drive changes in behaviour (e.g. among hunters) that affect risk of zoonotic transmission.	High	Longitudinal studies in high-risk areas or priority populations, spatial studies across gradients of environmental disturbance.
Host factors: Which host factors most strongly increase the risk of zoonotic spillover?	An understanding of biological vulnerabilities (e.g. immunosuppression or co-infection) will inform efforts to protect high-risk populations.	High	Case–control and cohort studies.
Behavioural factors: How do the knowledge, attitudes and practices of potentially vulnerable groups (e.g. women, hard-to-reach groups, indigenous communities) affect risk of zoonotic transmission?	Certain groups may be at higher risk of zoonotic infection because of behavioural or other factors. A deeper understanding will inform targeted and tailored prevention strategies.	Medium	Anthropology, zoo-anthropology studies.
Socio-cultural influences: What socio-cultural practices in endemic and non-endemic areas affect the risk of spillover?	An understanding of the socio-cultural practices that shape human, animal and pathogen interactions in both endemic countries and non-endemic will help to anticipate geographic expansion.	High	Socio-ecological and behavioural research, mixed-methods studies (qualitative plus quantitative) on hunting, wildlife trade, pet ownership, and cultural practices. Participative epidemiology and community engagement.
Environmental factors: Which environmental factors (land-use change, deforestation) most strongly determine the risk of MPXV spillover?	Changing land-use practices are likely to affect human–animal contacts and risk of spillover.	High	Environmental surveillance studies (water, soil, vectors).
Environmental disturbance and climate change			
Environmental disturbance: How will factors such as deforestation and land-use change and climate change affect MPXV spillover and spread?	Forest clearing and climate variability can be drivers of MPXV spillover from wildlife to humans. Gaps remain in understanding the relative influence of climate determinants. Evidence is needed to improve risk prediction and inform targeted surveillance and prevention strategies.	Medium	Retrospective data analysis from areas where outbreaks occurred to identify putative suitable regions for transmission based on bioclimatic factors. Integration of remote sensing data and modelling.
Extreme weather events: How might extreme weather events affect human–	Extreme weather events may bring humans and wildlife into closer contact, increase reliance on hunting and handling	Medium	Integrated analysis of epidemiological and weather data; modelling.

animal interactions and risk of MPXV transmission?	of wild animals, displace populations and create crowded living conditions, and disrupt disease surveillance and response systems. They might also alter the ecology of potential animal reservoirs.		
Warming: What impact will higher temperatures have on virus replication, survival and transmission, and on human–animal interactions?	Rising global temperatures may influence MPXV biology, environmental persistence and/or interactions between humans and animal reservoirs.	Medium	Experimental studies of viral sensitivity to temperature. Temperature-based models for predicting mpox outbreaks and integration of climate data into zoonotic spillover prevention strategies.
Displacement: How might population movements driven by climate change or other disrupters affect risk of zoonotic spillover?	Population movements can elevate zoonotic spillover risk by expanding human activity into natural habitats, creating crowded settlements with greater animal exposure, and redistributing hosts, vectors and pathogens across regions.	High	Modelling.
Prevention strategies			
Current practice: Which strategies are currently implemented to prevent animal-to-human transmission of mpox in endemic countries?	Understanding prevention strategies implemented in endemic countries can help assess their effectiveness in preventing spillover events.	High	Systematic review of strategies to prevent mpox transmission at the human–animal interface.
Community interventions: Which community-level interventions are most effective in reducing high-risk human–animal interactions, particularly those associated with hunting, handling and consumption of wild animals?	Community behaviours play a crucial role in increasing human–animal interactions and favouring disease transmission. Prevention strategies rooted in communities are important to reduce these high-risk interactions and prevent disease spillover.	High	Qualitative studies in endemic regions combining focus group discussions, key informant interviews and observations. Randomised controlled trials of co-developed interventions.
Leveraging surveillance: How can surveillance systems move from outbreak detection to proactive spillover prevention?	Shifting from proactive case-detection to investing in prevention at source requires investment in surveillance systems integrating different data sources to predict risk regions and proactively guide implementation of prevention strategies.	High	Cross-sectional studies to evaluate surveillance systems.

Policy shifts: What policy changes are needed to operationalise One Health approaches for mpox prevention in Africa?	The One Health approach is recommended in prevention of zoonotic diseases including mpox. Understanding the effectiveness of current policy and gaps is required for sustained implementation of this approach at the community, national and regional level.	High	Policy analysis combined with case-studies highlighting policies implemented at the country level.

ENABLERS:

Enablers	Rationale	Importance	Approach
Capacity, community tools/resources and other enablers that would accelerate closing of knowledge gaps or overcoming of key barriers	*How these enablers would accelerate development of medical countermeasures*	*Very high, high, medium or low*	*Strategy for developing enablers*
Surveillance systems			
Diagnostics for reservoir identification	Tools are needed to detect MPXV in animal hosts and to distinguish different clades.	Very high	PCR, metagenomics, serology, infectivity studies; analysis of archived samples from zoo animals.
Integrated One Health surveillance	It is impossible to address mpox zoonotic outbreaks without a One Health approach to surveillance. Not all reservoirs of mpox are fully established. Silent transmissions can cause unpredictable outbreaks and an absence of surveillance can make detection difficult. Relying solely on human cases will make epidemic preparedness and prevention of outbreaks challenging. An integrated approach is needed, covering the environment (e.g. sampling of hard surfaces (built or natural environments), waste/sewage water,	Very high	Surveillance of wildlife reservoirs and environmental sites; application of molecular tests and genomic sequencing.

	animal habitats, and human–animal interface settings) to improve early detection and tracking of virus circulation across wildlife, domestic animals, and human populations. It is also useful for hotspot detection and intervention prioritisation, and for risk perception.		
Integrated data analysis	Integration of data from different sources will improve understanding of transmission pathways, support the predictability of hotspots and viral evolution across species, promoting outbreak preparedness.	High	Comparative genomic studies. Statistical modelling to assess patterns and detect trends in surveillance data.
Paired or contemporaneous sampling of humans and wildlife	Strengthens understanding of transmission pathways and ability to detect sustained human transmissions and true spillover events. Critical for early warning events.	High	Real-time/joint One Health surveillance incorporating rapid point-of-care tests. Comparative genomic studies.
Data use to inform policy and prevention strategies	Stronger linkage between researchers and policymakers will support more evidence-based policies and actions.	High	Data sharing, visualisation and triangulation
Standardised case definitions for mpox in animals	Countries have established case definitions for mpox in humans, but not for mpox in animals. A standardised case definition is needed to support reliable identification of MPXV in animal hosts.	Very high	Systematic review, diagnostic accuracy studies.
Stakeholder engagement			
Enhanced collaboration between scientific institutions and governments and regional bodies	Research activities need to be linked with public health activities to ensure evidence generated by research informs public		Risk mapping, collaboration, consultations on preferred information delivery approaches. *See also Diagnostics section*.

	health interventions to prevent zoonotic transmission, bridging the divide between science and policy. Involvement of regional bodies such as Africa CDC can promote consistent practice across countries and international coordination.		
Private sector involvement	Could support development of diagnostics and other tools to track MPXV.		Co-design of solutions based on local needs (including low-tech and cold chain free). Build collaborative exchanges with local health workforce to enhance acceptability of technology deployment.
Wildlife traders	Consumption of wildlife and its trade are important risk factors for mpox transmission. Wildlife traders are therefore important stakeholders in mitigating mpox transmission. Animal products are also used as zootherapy and could be risk factors for MPXV transmission.		Build understanding of current practices and perceptions. Communicate safe practices around wildlife trade to reduce the risk of transmission. *See also Social and Behavioural Sciences section.*
Community involvement: Promoting community ownership of mpox challenge to reduce risky behaviours and facilitate community-based surveillance.	A greater sense of community ownership will be central to control strategies and epidemiological surveillance.		Social anthropology, community involvement and participation, involvement of traditional leaders. Communication with communities around mpox case identification and reporting. *See also Social and Behavioural Sciences section.*
Capacity building			
Equitable research partnerships	Where resources and publications are equally shared between global south and global north collaborators, to increase visibility of researchers and the division of research between partners. Ownership of samples and viral isolates as an important part in international collaborations.		Formal collaboration agreements that ensure balanced leadership roles, shared decision-making. Joint protocols for data sharing, biobanking and material transfer that recognise local ownership of samples and viral isolates. Promoting joint dissemination strategies.

Training and skills development	Guidelines and diagnostic tools for reservoir surveillance are needed to support training of local researchers and practitioners.		Invest in training in endemic settings.
Epidemiology and modelling capacity	Additional human capacity is needed to collect and analyse epidemiological data (including genomic data) and to present to policymakers in an actionable format.		Invest in capacity building in endemic settings. Leverage recent investments in capacity building by global funders.
Biobanking and sample repositories	Infrastructure is needed to store samples and facilitate research that is not dependent on external funding.		Invest in local infrastructure and institutional support.
Sample and data access			
Open science practices	Institutions and researchers in some settings are unable to access resources and databases especially around genetic analyses.	Very high	Promote use of open science practices in all research activities.
Sample and data sharing	Accessible and fair sharing of MPXV genomic resources. Application of the Nagoya protocol convention on biological diversity.	High	Collaboration, compensation and technology transfer agreements.

1.2 Epidemiology and evolution

Mpox was largely restricted to sub-Saharan Africa until 2003, when cases of human mpox associated with animals imported from West Africa were reported in the USA. In 2017, Nigeria witnessed a resurgence of mpox, 38 years after the last case was reported in 1978. Following this outbreak, subsequent travel-related exportations of mpox from Nigeria to several countries occurred between 2018 and 2021.

In May 2022, sustained transmission of **clade IIb** MPXV was reported on a global scale within dense sexual networks, which was followed by unprecedented expansion of **clade Ib**, marked by sustained human-to-human transmission within Africa. Genomic investigations of the 2022 global outbreak revealed signs of microevolution compared to earlier reference genomes. Notably, mutation patterns consistent with host **APOBEC3-mediated editing** have been reported[13], highlighting the potential for viral adaptation, altered transmissibility and antigenicity, and possible impacts on diagnostics and immune escape.

The recent detection of **inter-clade recombinant viruses** (Ib/IIb) in the UK and India in 2025 and 2026 highlights other potential mechanisms of evolution and further complicates diagnostic interpretation[18]. WHO has highlighted the presence of **genomic mosaicism** in these inter-clade recombinant strains, raising concerns about their potential wider circulation[19].

These events have highlighted gaps in surveillance, diagnostics and outbreak preparedness. Thus, robust research on MPXV evolution is critical for detecting functionally relevant genomic changes and for interpreting phylogenetic signals detected in outbreak investigations. Although some genomic characterisation is occurring, genomic surveillance is not yet being systematically applied to MPXV in low-resource/high-burden settings.

Research on mpox epidemiology and virus evolution is important for historically endemic regions and for the broader global community. In non-endemic settings, timely epidemiological and genomic data enable rapid case detection, contact tracing, and targeted public health interventions that limit onward spread; in historically endemic countries, longitudinal surveillance is required to characterise animal reservoirs, spillover dynamics and the drivers of sustained human-to-human transmission. Knowledge from epidemiological and evolutionary studies will directly improve detection and response by:

- Enabling **earlier identification of transmission chains and geographic spread** through genomic and case-based surveillance.
- Informing **refinement of diagnostics and genomic assays** to maintain sensitivity and specificity in the face of viral evolution.
- Guiding **vaccine and therapeutic strategies** through better characterisation of antigenic and phenotypic variation.
- Supporting **evidence-based public health policies and risk communication** tailored to both endemic and non-endemic contexts.

[18] Pullan ST, Everall I, Doherty R et al. Inter-Clade Recombinant Mpox Virus Detected in England in a Traveller Recently Returned from Asia. December 2025. Available at: https://virological.org/t/inter-clade-recombinant-mpox-virus-detected-in-england-in-a-traveller-recently-returned-from-asia/1015.

[19] WHO. Mpox: recombinant virus with genomic elements of clades Ib and IIb – Global. 14 February 2026. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/2026-DON595

Therefore, sustained investment in laboratory capacity, data sharing and integrated One Health surveillance, particularly in historically endemic countries, is essential to strengthen global mpox preparedness and control.

Further, sustained MPXV transmission within particular social and sexual networks, including historically stigmatised populations, has highlighted the need for equitable, stigma-free public health strategies that ensure access to prevention and care for marginalised populations[20].

[20] Wannigama DL, Amarasiri M, Phattharapornjaroen P et al. Community-based mpox and sexually transmitted disease surveillance using discarded condoms in the global south. Lancet Infect Dis. 2024;24(10):e610-e613. doi: 10.1016/S1473-3099(24)00514-0.

KNOWLEDGE GAPS:

Subtheme 1: Disease burden and distribution			
What is the true mpox disease burden and how is it distributed?			
Knowledge gap	**Rationale**	**Importance**	**Approach**
Instruction: Brief description of knowledge gap/research priority	*Statement of why this knowledge gap is important and how closing it would advance MCM development or implementation*	*Very high, high, medium or low*	*Types of study that could address knowledge gap*
Disease burden: What is the true burden of mpox in endemic countries and how does it vary by age, sex and clade?	Accurate burden estimates are essential for risk assessment, resource allocation and vaccine strategy development. However, surveillance systems in endemic regions are often fragmented, with under-reporting and limited laboratory confirmation. Standard surveillance also misses many cases due to the effects of stigma on health-seeking behaviour. Wastewater sampling can provide an early warning and unbiased prevalence estimates.	High	Population-based serosurveys; enhanced case-based surveillance; community cohort studies; capture–recapture analyses; integration of routine surveillance with genomic sequencing. Establishment of registries to collect clinical information on confirmed cases. Wastewater-based epidemiology (WBE): Sequential sampling of municipal wastewater; correlation of viral loads with reported case counts; genomic sequencing of wastewater samples.
Population immunity: What is the current level of population immunity arising from previous smallpox vaccination, prior mpox infection or mpox vaccination, and how does this vary by geography, age group and viral clade?	Mpox epidemiology will be dependent on population immunity, which will be affected by prior smallpox (pre-1980s) or mpox vaccination and MPXV infection. An understanding of population immunity will be important for modelling future outbreak risk and informing vaccination strategies.	High	As above, with modelling to explore potential outbreak scenarios and to evaluate possible vaccination strategies.

Transmission pathways: What are the key routes of transmission of different MPXV clades?	Accurate information on differences in natural history of infection by clade would indicate whether clade-specific control strategies are needed.	High	Detailed epidemiological investigations; integration of routine surveillance with genomic sequencing; phylogenetic reconstruction of transmission chains.
Large-scale epidemiology: What social, climatic and environmental factors influence the geographic distribution of MPXV?	Social, environmental and climatic factors potentially influencing MPXV epidemiology are poorly understood. Deeper understanding will support preparedness planning and early warning systems in both historically endemic and non-endemic regions.	Medium	Ecological modelling; climate-linked risk mapping; spatial epidemiology; integration of land-use change data.
Subtheme 2: Transmission dynamics			
What are the key drivers of sustained human-to-human transmission?			
Key drivers: What are the main drivers of sustained clade Ia/Ib and IIb human-to-human transmission?	The 2022 global outbreak demonstrated efficient transmission in new social and sexual networks and individual biological factors affecting the risk of transmission (e.g. viral persistence in semen). Determinants of sustained human-to-human transmission require clarification. Identifying transmission drivers informs targeted prevention strategies and behavioural interventions.	Very high	Detailed epidemiological investigations; network analysis; longitudinal shedding cohorts (semen/rectal); behavioural surveys; phylogenetic reconstruction of transmission chains; transmission modelling.
Environmental persistence: What is the contribution of environmental persistence and fomites to MPXV transmission?	The role of contaminated surfaces (soiled bedding, healthcare or homecare settings) in non-sexual transmission is poorly understood. A deeper understanding would inform infection prevention and control (IPC) guidelines and practices.	Medium	Surface sampling in households and hospitals; viral persistence and disinfection studies under various environmental (temperature/humidity) or geographical contexts; environmental DNA/RNA tracking; linkage to epidemiology/transmission data to inform infection prevention and control practices.
Asymptomatic infections: What role do asymptomatic/subclinical MPXV infections play in disease transmission?	Asymptomatic MPXV infection may contribute to cryptic transmission but its extent remains uncertain. Clarification would have implications for outbreak	High	Prospective contact studies; sero-epidemiological surveys; PCR and seroconversion screening of high-risk contacts; household transmission studies.

	modelling, contact-tracing policies and risk communication.		
Transmission pathways: What are the key patterns of onward transmission in different clinical and non-clinical settings?	Various clinical and non-clinical settings, including households, healthcare facilities, schools, prisons, refugee/displaced people facilities and sexual networks, may be associated with particular patterns of MPXV transmission. Understanding these pathways will inform the design of preventative interventions tailored to specific settings.	High	Detailed epidemiological investigations; network analysis; behavioural surveys; phylogenetic reconstruction of transmission chains; transmission modelling.
Other infections: How does the presence of co-infections/co-morbidities affect MPXV transmission?	The natural history of infection may be affected by interactions with other endemic infections in addition to HIV, including viral hepatitis and parasitic infections such as malaria, which are common in many mpox-affected areas. Co-infections could potentially affect both mpox susceptibility and infectivity.	High	Longitudinal shedding cohorts.
Reinfection: What factors affect the risk of MPXV reinfection?	Natural immunity provides protection against reinfection but cases of reinfection have been described and the duration of natural (and vaccine-induced) protection remains unclear. Natural infection typically provides strong cross-clade protection but less is known about long-term protection.	High	Long-term cohort studies.
Stigma: How does stigma affect health-seeking behaviour and transmission dynamics?	Stigma may discourage testing and hinder contact tracing, particularly in MSM and sex worker communities. Understanding these barriers is key to effective public health messaging.	High	Qualitative semi-structured interviews; community-led surveys; longitudinal behavioural tracking; assessment of 'health-seeking' delays. *See also Social and Behavioural Sciences section.*
Subtheme 3: Viral evolution and adaptation			
How is MPXV evolving in human populations?			
Population genomics: What are the temporal and spatial patterns of MPXV evolution?	Mapping genetic diversity within MPXV clades and lineages across regions will shed light on MPXV evolutionary dynamics and emergence of particularly problematic variants.	Very high	Viral whole genome sequencing; phylogenomic analyses.

Mutational dynamics: How is MPXV evolving in human populations?	Genomic analyses suggest microevolution and APOBEC3-associated mutation patterns, but functional consequences remain unclear. Evolutionary changes could affect transmissibility, virulence, diagnostic accuracy, and vaccine effectiveness.	High	*See Human–Pathogen Interactions section.*
Recombination: How significant are genome recombination events to mpox dissemination?	Cross-clade recombination has been observed but its frequency and potential implications for mpox evolution remain unclear.	High	As above.
Subtheme 4: Functional consequences			
What are the implications of MPXV evolution?			
Biological impact: How does genetic diversity affect MPXV transmissibility, clinical severity and medical countermeasures?	Comparative studies between clade I and clade II viruses remain incomplete. Important for understanding differences in transmissibility, severity and intervention effectiveness.	Very high	*See Human–Pathogen Interactions section.*
Subtheme 5: Data for action			
How can epidemiological data best be delivered to policymaking to inform disease control and decision-making?			
Data timeliness: How can the timeliness and accessibility of epidemiological data for decision-making be improved?	Outbreak response depends on rapid interpretation of case trends, transmission patterns and geographic spread. However, in many settings – particularly endemic regions – data reporting, validation and analysis are delayed. These delays limit the ability of policymakers to implement timely interventions such as vaccination strategies, targeted risk communication, or infection prevention measures. Bridging the gap between surveillance data and actionable insights is critical for early outbreak control and resource allocation	Very high	Develop real-time digital surveillance dashboards integrating epidemiological, laboratory and genomic data. Establish standardised reporting pipelines linking surveillance systems with national public health emergency operations centres. Use automated analytics and outbreak alert thresholds to rapidly flag increases in transmission. Integrate decision-support tools that translate epidemiological indicators (incidence, reproduction

			number, cluster detection) into recommended response actions.
Metrics: How can complex epidemiological and genomic data be translated into policy-relevant indicators?	Policymakers often require concise, interpretable metrics rather than detailed epidemiological analyses. However, genomic surveillance, transmission modelling, and behavioural studies generate complex datasets that may not easily translate into policy decisions. Without clear synthesis and interpretation, valuable data may remain underutilised in policy processes.	Medium	Develop standardised epidemiological indicators for mpox policy decisions (e.g. outbreak thresholds, geographic risk classification). Produce regular policy briefs and situational reports translating surveillance findings into recommended actions. Integrate genomic and epidemiological analyses to inform guidance on diagnostics, vaccination strategies and outbreak control. Establish multidisciplinary data interpretation units within national public health institutes.
One Health: How can multi-sectoral data be integrated to support One Health decision-making?	Mpox is a zoonotic disease with ecological, environmental and human transmission components. Fragmented data systems across sectors limit understanding of spillover dynamics and hinder coordinated policy responses. Integrating data from human health, wildlife surveillance and environmental monitoring is essential to inform prevention strategies and identify emerging risks	High	Establish interoperable One Health surveillance platforms linking human, veterinary, and environmental data. Develop shared analytical frameworks and dashboards across ministries and agencies. Implement joint risk assessments involving epidemiologists, veterinarians and environmental scientists. Formalise cross-sector data-sharing agreements and governance mechanisms.
Prioritisation: How can evidence best be translated to support resource allocation and intervention prioritisation?	Decision-makers must allocate limited resources across multiple health priorities. Epidemiological data are critical for identifying high-risk populations, determining geographic prioritisation, and evaluating intervention effectiveness. However, the types of evidence required for policy decisions – such as cost-effectiveness analyses, burden estimates and risk projections – are often lacking or not tailored to policymaker needs.	High	Integrate epidemiological modelling and health-economic analyses to inform vaccination and intervention strategies. Develop risk-based prioritisation frameworks for vaccination and surveillance. Conduct policy-focused modelling scenarios to evaluate the impact of potential interventions. Generate evidence summaries tailored for ministries of health and finance.

Communication: How can epidemiological evidence best be communicated during outbreaks?	Effective disease control requires not only data generation but also clear communication. Misinterpretation of epidemiological findings may delay policy responses or contribute to misinformation. Structured communication mechanisms are needed to ensure that scientific evidence is conveyed accurately and rapidly to decision-makers and communities.	High	Establish formal science-to-policy communication mechanisms between research institutions and ministries of health. Develop standardised outbreak situation reports and briefing formats. Train epidemiologists in policy communication and risk communication strategies. Use interactive dashboards and visualisation tools to improve interpretability of surveillance data. *See also Social and Behavioural Sciences section.*

ENABLERS:

Enablers	Rationale	Importance	Approach
Capacity, community tools/resources and other enablers that would accelerate closing of knowledge gaps or overcoming of key barriers	*How these enablers would accelerate development of medical countermeasures*	*Very high, high, medium or low*	*Strategy for developing*
Genomic surveillance			
Strengthened genomic surveillance capacity (endemic and non-endemic countries)	Enables real-time tracking of viral evolution, clade differentiation, transmission chains and clade distribution; improves understanding of mutation patterns and adaptation. Detects variants that may affect vaccine, diagnostic or antiviral performance; informs strain selection and assay refinement.	Very high	Invest in sequencing platforms in endemic countries; regional sequencing hubs; standardised protocols; training bioinformaticians; sustainable reagent supply chains. Ensure data are rapidly shared with policymakers and frontline healthcare workers.
Integrated One Health surveillance			
Integrated One Health surveillance systems	Links human, animal and environmental data to clarify reservoirs and spillover dynamics. Identifies zoonotic drivers that inform preventive strategies beyond vaccines (e.g. reservoir control, risk reduction).	High	Establish cross-sectoral data-sharing agreements; joint wildlife–human surveillance programmes; harmonised reporting frameworks; policy-level coordination mechanisms.
Climate and ecological modelling capacity	Identifies environmental drivers and geographic risk expansion. Informs strategic stockpiling, vaccination prioritisation, and early warning for at-risk populations.	Medium	Build modelling units within national institutes; cross-training of epidemiologists and climate scientists; integration with public health emergency operations centres.
Wastewater and environmental surveillance infrastructure	Provides an unbiased 'early warning' system that does not depend on individual health-seeking behaviour. Essential for sites such as urban centres and displaced person camps.	Medium	Standardise MPXV extraction protocols for sewage; integrate environmental data into national epidemiological dashboards; provide low-cost sampling kits to municipalities.
Policy support functions			
Health economics and cost-effectiveness modelling units	Policymakers face competing priorities and need local data on the cost-effectiveness of vaccination, surveillance and treatment to justify investment. Without economic evidence, mpox may remain	Medium	Embed health economists in national public health institutes (or regional bodies like Africa CDC); develop standardised costing tools for mpox interventions (surveillance, vaccination,

	deprioritised against HIV, malaria, TB and other diseases, even during outbreaks.		treatment, IPC); generate local data on cost-per-case-averted, cost-per-DALY-averted, and budget impact; train local economists in infectious disease modelling; produce policy briefs tailored to finance and health ministries.
Social science and behavioural research task forces	Biological data alone cannot stop transmission if stigma prevents people from seeking care. Behavioural insights drive better uptake of vaccines and contact tracing.	High	Embed social scientists within rapid response teams; create standardised 'stigma-monitoring' surveys; partner with local civil society (e.g. sex worker or MSM networks).
Sustainable laboratory networks			
Sustainable laboratory networks (PCR, serology, neutralisation)	Improves detection accuracy and reduces underdiagnosis. Ensures reliable endpoints for vaccine and therapeutic evaluation; monitors diagnostic performance over time.	Very high	Strengthen regional reference labs; proficiency testing schemes; supply chain resilience planning. Ensure responsiveness to emerging genomic data.
Serological assay standardisation and reference reagents	Multiple serological assays exist (ELISA, neutralisation, multiplex), but results are often not comparable across studies. This hampers meta-analyses, identification of correlates of protection, and vaccine comparisons. Without standardised reagents and protocols, data from vaccine effectiveness studies cannot be pooled or compared.	High	Convene international consortium (WHO, academia, industry) to: (1) develop international reference standards (e.g. WHO International Standard for anti-MPXV antibodies); (2) validate assays against common panels of well-characterised sera; (3) distribute control panels and reagents to labs globally at low cost; (4) establish external quality assessment (EQA) schemes.
Decentralised point-of-care (POC) diagnostic networks	Current reliance on central labs (PCR) causes weeks of delay in rural/endemic areas. POC tests enable immediate isolation and clinical management.	Very high	Validate and roll out LAMP or CRISPR-based rapid assays; establish 'last-mile' reagent supply chains; train community health workers in field testing. Ensure data are connected to surveillance systems and samples are transferred to reference facilities.
Longitudinal cohort platforms in endemic regions			
Longitudinal cohort platforms in endemic regions	Can provide robust incidence, immunity and transmission data, short-, medium and long-term outcomes and complications data, and clarifies asymptomatic infection rates. Can generate natural history and immunological data required for	High	Create standing clinical research multi-country prospective cohorts; integrate with primary healthcare; ethical pre-approval frameworks for rapid activation during outbreaks.

	vaccine and therapeutic evaluation and correlates of protection.		
Data sharing platforms and real-time analytics	Facilitates rapid global analysis of epidemiological and genomic trends. Supports coordinated global response and adaptive modification of diagnostics or vaccines.	High	Secure interoperable databases; FAIR data principles; incentives for rapid data deposition; global dashboards integrating epidemiology and genomics.
Harmonised case definitions and data standards	Improves comparability of epidemiological data across countries and outbreaks. Strengthens pooled analyses for vaccine effectiveness and therapeutic trials.	High	WHO-led development of standardised protocols; digital reporting platforms; training and compliance monitoring.
Biobanks and standardised specimen repositories			
Biobanks and standardised specimen repositories	Ensures availability of well-characterised samples across clades and timepoints for evolutionary and immunological studies. Enables rapid evaluation of vaccine-induced immunity, neutralisation breadth, and diagnostic sensitivity.	High	Develop national and regional biorepositories; standardise consent and governance; ensure equitable access and benefit-sharing agreements.

1.3 Diagnostics

Diagnostics are critical for clinical care and epidemiological surveillance (including One Health/environmental surveillance). Different diagnostic use cases will have different requirements, which need to be clearly defined. Important considerations include the **breadth of detection** – diagnostics may be designed to detect multiple orthopoxviruses, just MPXV or distinguish specific MPXV clades/genetic variants. **Target product profiles** for mpox diagnostics were developed by WHO in 2023[21].

Notable progress has been made in the mpox diagnostic landscape, with 12 products now WHO-prequalified; recent policy amendments have opened up pathways for affordable point-of-care tests. However, the current diagnostic portfolio is heavily weighted toward **laboratory-based molecular assays** requiring sophisticated equipment, trained personnel and stable electricity – resources often unavailable in outbreak epicentres. There is an urgent need for:

- **Rapid lateral flow antigen tests**: Deployable at the community level, requiring minimal training, with results in 15–30 minutes.
- **Near point-of-care molecular tests**: Affordable, portable molecular platforms suitable for use at decentralised sites and implementation in low-resource settings.
- **Multiplex assays**: Tests capable of detecting multiple orthopoxviruses while differentiating MPXV, including MPXV clades, and multi-virus tests for differential diagnosis.

However, significant gaps persist across development, evaluation, regulation and implementation that limit the availability and deployment of diagnostics where they are most needed. Manufacturers, particularly smaller companies and academic developers, face significant barriers, including:

- **Target antigen selection**: The need to balance specificity (MPXV-specific targets) versus pan-orthopox detection to account for antigenic conservation across strains presents technical challenges.
- **Unclear regulatory pathways**: Confusion about requirements for WHO pre-qualification versus Africa CDC approval and lack of harmonisation creates duplication of effort and delays market entry.
- **Rapid outbreak dynamics**: By the time a test is developed and approved, outbreak waves may have subsided, reducing commercial viability and manufacturer interest.
- **Limited market size**: Mpox, while of public health concern, represents a small market compared to diseases such as TB or malaria, reducing investment incentives. Nevertheless, mpox cases are being detected in multiple countries, emphasising the global reach of this pathogen despite its characterisation as a limited market.

These factors contribute to an **accessibility challenge**: Several WHO-prequalified diagnostics are not readily accessible in high-burden settings such as Africa. Products may be approved but remain unavailable due to procurement barriers, lack of distribution networks, or insufficient market incentives for manufacturers. Ensuring production can cope with surges in demand during outbreaks is a further key challenge.

[21] https://www.who.int/publications/i/item/9789240076464

KNOWLEDGE GAPS:

Subtheme 1: Diagnostic design			
How can the design of new MPXV antigen and molecular diagnostics be optimised?			
Knowledge gaps	**Rationale**	**Importance**	**Approach**
Brief description of knowledge gap/research priority	*Statement of why this knowledge gap is important and how closing it would advance MCM development or implementation*	*Very high, high, medium or low*	*Types of study that could address knowledge gap*
Antigen selection: Which antigens should be included in tests?	Manufacturers face uncertainty regarding which viral antigens provide optimal sensitivity across clade I and clade II variants while minimising cross-reactivity with non-pathogenic orthopoxviruses. Minimal antigenic divergence (2-3 amino acids) across orthopoxviruses complicates target selection. Single-target designs risk strain-specific dropouts as the virus evolves. This uncertainty delays product development and creates regulatory approval challenges when evaluators expect clade differentiation but manufacturers design pan-orthopoxvirus assays.	High	Update WHO/Africa CDC target product profiles to explicitly define acceptable target strategies (mpox-specific vs pan-orthopox vs multiplex) per use case, resolving regulatory ambiguity. Conduct comparative genomic and proteomic analyses to identify conserved epitopes. Run validation studies comparing multi-target and single target designs on diverse clinical specimens from both clades. Develop feedback loops to engage end-user experience with tests at a programmatic level.
Clade differentiation: What are the essential and preferred characteristics of mpox diagnostics?	While not initially required, differentiation of MPXV clades I and II is now preferred but not uniformly available across all approved platforms, limiting epidemiological surveillance capacity.	High	Update the 2023 WHO TPPs to designate clade I/II differentiation as a preferred (not merely desirable) specification for near-POC and laboratory-based assays. Develop a consensus document through WHO/Africa CDC clarifying the minimum analytical requirements for clade differentiation and acceptable methods for validation.
Multiplex assays: What are the essential and preferred characteristics of multi-virus diagnostics?	Tests capable of detecting multiple orthopoxviruses while differentiating mpox reduce the risk of false negatives due to strain variation. Multiplex assays	Medium	Update WHO TPPs to define the clinical value proposition for multiplex assays (e.g. mpox + varicella + HSV). Clarify regulatory pathway for multiplex EUL submissions since manufacturers

	also provide opportunities to identify pathogens often present as co-infections with MPXV.		currently face uncertainty on whether pan-orthopox detection is a feature or a liability. **Co-infections**: Diagnostic performance during co-infections (e.g. mpox + HIV, mpox + varicella, mpox + HSV) requires specific evaluation. The effect of one virus on detection of another is not well characterised and should be included in multiplex validation study designs. Diagnostic design could also consider incorporating bacterial pathogens such as *Treponema* (syphilis) often present as co-infections in some key populations. **Poxvirus recombinants**: Given the known propensity of poxviruses to recombine, test designs should account for potential novel recombinants (e.g. between mpox and vaccinia). Pan-orthopox assays may provide such functionality but require monitoring as new variants are identified.
Cross-reactivity interpretation: What approaches should be adopted in epidemic vs sporadic contexts?	Pan-orthopox tests detect multiple orthopoxviruses (vaccinia, cowpox, MPXV) due to minimal antigenic divergence. Where there is a high pre-test probability of mpox (e.g. outbreak settings), a pan-orthopox positive test may support a presumptive mpox diagnosis, but testing algorithms should define when MPXV-specific PCR or sequencing confirmation is required, particularly for index cases, low-prevalence settings, vaccinated populations, patients with possible vaccinia exposure, or unusual clinical or epidemiological patterns. By contrast, in low-prevalence or post-elimination settings, false positives from cross-reactive orthopoxviruses could trigger unnecessary outbreak responses. Current guidance does not clearly delineate when confirmatory molecular testing is required	Medium	Develop context-specific testing algorithms: epidemic settings (sustained transmission) permit antigen-based presumptive diagnosis without molecular confirmation; sporadic settings require PCR confirmation of positive antigen tests. Conduct serosurveys and environmental sampling to characterise local orthopoxvirus ecology and cross-reactivity risk. Establish clinical case definitions incorporating epidemiologic likelihood alongside laboratory results.

	or presumptive antigen-based diagnosis is sufficient.		
User input: How can the needs of end-users (community health workers, clinicians, surveillance officers) inform the design of new mpox diagnostics?	Point-of-care tests designed without input from intended users frequently fail due to issues with ease of use, waste generation, connectivity or interpretation in field conditions.	Medium	Conduct policymaker and health worker consultations to define use-case requirements that feed directly into TPP revision.

Subtheme 2: Evaluation			
How can standardised specimen collection and evaluation mechanisms be developed to deliver comparable and reliable data on text performance?			
Knowledge gaps	**Rationale**	**Importance**	**Approach**
Specimen collection: What is the optimal approach for specimen collection that minimises variability?	Lesion material is the preferred diagnostic specimen. Alternative specimens, such as oropharyngeal/nasopharyngeal swabs and saliva, should be evaluated as options for research or explicitly defined use cases, particularly when lesions are absent, but should not be considered validated tools for routine asymptomatic screening or quarantine decisions until diagnostic performance and correlation with infectiousness are established.	High	First, develop standardised specimen collection SOPs with training videos demonstrating proper swabbing technique, and include visual guides for lesion identification and stage assessment. Second, conduct additional validation studies comparing lesion swabs with alternative specimen types, including nasopharyngeal swabs and saliva, specifically for antigen-based assays. Swabbing technique (pressure, duration, lesion type: crusted vs vesicular), sample adequacy, and specimen type (roof/base of lesion, oropharyngeal, blood) all independently affect antigen yield. This variability is a primary reason why test results using archived samples differ from those based on fresh field samples – collection conditions are rarely documented. Nasopharyngeal swab testing should be explicitly validated for pre-lesion detection in the exposure/incubation window – virus is detectable approximately 4 days before lesions appear. This has specific relevance for: (1) asymptomatic contact and family member surveillance; (2) healthcare worker screening; (3) quarantine decision-making. Validation studies should treat nasopharyngeal

			swab-based early detection as a distinct use case, not merely an alternative to lesion swabs.
Sample source: How can variability linked to sample source (fresh vs archived) be minimised?	The lack of standardised evaluation panels with defined viral load ranges further limits comparability across assays and evaluation sites. For example, a rapid lateral flow test evaluated on fresh samples in DRC/Uganda showed >70% sensitivity but was not approved by Africa CDC following testing on archived samples. PCR can detect nucleic acid long after antigen has degraded, making PCR-anchored evaluation of archived specimens systematically unfair to antigen tests.	Very high	Develop standardised evaluation panels using well-characterised archived specimens representing previously defined viral load ranges and specimen types to enable comparable multisite performance assessments. Importantly, the composition of storage buffer used for archived samples may introduce variability in assay performance; therefore, this factor should be assessed and controlled when evaluating diagnostic tests using archived samples. Develop explicit guidance on gold standard selection: when PCR is the comparator for archived specimens, minimum viral load thresholds should be specified to exclude samples where antigen is likely degraded. Where feasible, evaluate RDTs on fresh samples during active outbreaks via pre-established evaluation hubs.
Evaluation: How can comparable and reliable data on test performance be generated to inform decision-making?	Due to variation in evaluation methodologies, data on different devices are hard to compare, affecting programmatic decision-making on choice of test/platform.	Very high	As above. Regional/subregional centres could provide technical support to ensure consistent evaluation, conduct evaluations and quality assure diagnostics centres.

Subtheme 3: Deployment			
How can diagnostic tools best be deployed in clinical care and surveillance systems?			
Knowledge gaps	**Rationale**	**Importance**	**Approach**
Integration with clinical care: How can use of diagnostic tests in clinical care be optimised?	Clarity is needed on how and when diagnostics should be used in clinical practice to guide clinical care.	High	Review existing practice and develop consensus case management pathways – clear protocols for how diagnostic results inform patient isolation, contact tracing and treatment decisions.
Integration with surveillance: How can linkage between laboratory diagnostics and surveillance systems (and implementation programmes) be strengthened?	Rapid diagnostic tests are commonly interpreted visually, introducing additional variability in results interpretation and further limiting systematic data capture and real-time programme monitoring.	Medium	Conduct operational research to identify examples of good practice. Link diagnostic deployment to surveillance platforms (e.g. integrated disease surveillance and response, IDSR) and ensure real-time reporting.

			Digital reader technologies could further standardise the interpretation of rapid tests and support the automated transmission of results into surveillance systems for real-time monitoring. Develop or integrate with real-time data dashboards for health officials and programme managers, enabling geospatial tracking of positivity rates and response indicators.
Self-testing: What is the role of self-testing in mpox diagnosis and surveillance?	Self-testing in community settings could enable rapid mass testing at scale and help to address barriers to care-seeking associated with stigma.	Medium	The self-testing approach must include a clear linkage-to-care pathway: individuals testing positive require accessible guidance on isolation, notification of contacts, and referral to clinical care. Consider requiring that TPP specifications for home-use formats include a linkage mechanism (e.g. QR code on packaging directing to national guidance, SMS-based reporting, or integration with community health worker follow-up systems). Commission social research on acceptability of mpox self-testing, particularly in MSM and sex worker communities where stigma is high. Link findings to TPP revision for home-use format specifications. *See Social and Behavioural Sciences section.*
Community acceptability: What are the attitudes of communities to use of mpox diagnostics?	Diagnostic deployment must consider community trust, stigma and health-seeking behaviour to ensure acceptance and uptake.	Medium	Commission formative social research on acceptability of mpox testing (including self-testing) across key affected populations. Findings to be shared with the social and behavioural science working group and fed into TPP human-factors requirements. Include community representatives in diagnostic coordination platform governance.

ENABLERS:

Enablers	Rationale	Importance	Approach
Capacity, community tools/resources and other enablers that would accelerate closing of knowledge gaps or overcoming of key barriers	*How these enablers would accelerate development of medical countermeasures*	*Very high, high, medium or low*	*Strategy for developing enablers*
Data sharing and pathogen access			
Specimen sharing: Ensuring equitable access to specimens for test development	Rapid specimen mobilisation and pathogen sharing are essential for diagnostic development but face significant barriers. The WHO Pathogen Access and Benefit Sharing (PABS) annex provides a framework, but implementation challenges remain.	Very high	Enable rapid specimen mobilisation in line with PABS annex, with explicit benefit-sharing commitments embedded in material transfer agreements. Benefit sharing should extend to both material generators (countries/institutions providing specimens) and innovators, ensuring dividends from diagnostics developed using those materials flow back equitably.
Specimen collections: Ensuring availability of quality-assured and standardised materials for developers	Availability of well-characterised specimens can be a barrier to diagnostic development.	Very high	Establish regional biobanking networks with governance structures enabling controlled access to specimens for manufacturer validations and independent evaluations while protecting donor rights. WHO/FIND/reference laboratories to co-create a repository of quantified mpox antigens and genomic materials (both Clade I and II) distributed to developers at low or no cost, tied to the diagnostic development support hub (see below). Existing biobanks should be mapped and supported to remain functional; where gaps exist, new biobanks should be established. Once mapped, material transfer frameworks should be put in place to support movement of samples to and between biobanks. Consent frameworks must be broad enough to cover material transfer agreements to any centre of excellence with capacity to conduct the required R&D, not limited to named institutions. Broader consent frameworks should be backed up by transparent governance mechanisms.
Ethical framework: Expediting use of samples for the public good	Current ethics protocols typically approve specimen use for specific technologies. When new diagnostic technologies	High	Develop overarching ethical approvals allowing archived samples to be used for future diagnostic evaluations without technology-specific re-approval.

	become available, archived specimens cannot be used for validation studies without returning to ethics committees for amended approvals. This leads to delays (6–12 months for re-approval), redundant specimen collection during outbreaks (creating ethical concerns about unnecessary procedures), and inefficient use of valuable archived repositories.		Develop model overarching consent frameworks allowing broad consent for future diagnostic technology development and validation rather than technology-specific approvals. Provide ethics committee guidance on balancing specimen donor autonomy with public health value of archived specimens. Consenting frameworks should be sufficiently broad to enable sample transfer to any qualified centre of excellence for future R&D purposes, not restricted to specific institutions or geographies. Benefit-sharing arrangements must be defined at the consent stage so that material generators share in outcomes.
Standardisation and evaluation methodologies			
Guidance: Global guidance for developers on device evaluation	Evidence-based, standardised evaluation protocols are needed that balance rigour with real-world relevance	Very high	Develop best-practice guidance on diagnostic evaluation methodologies, explicitly addressing: (1) criteria for when fresh vs. archived samples are appropriate; (2) gold-standard selection for different test types; (3) minimum sample size and statistical power requirements. Without standardised evaluation protocols, results from different sites cannot be compared or bridged, creating redundant evaluations. The fresh vs archived sample debate cannot be resolved without explicit guidance on which standard applies when.
Quality assurance: Regional/global EQA mechanisms	Reference standards are needed to enable developers to rigorously assess performance	High	Bolster EQA/proficiency testing panels for mpox diagnostics and distribute to participating laboratories, incorporating learnings from prior work. Establish and institutionalise a regional external quality assessment programme for mpox diagnostics by developing standardised EQA panels with characterised positive and negative specimens across different viral loads, clades and specimen types. Create and maintain accessible repositories of reference materials, strengthen regional distribution systems, and appoint regional EQA coordinators to distribute panels and provide feedback. Reference materials are inconsistently available, particularly between outbreak periods, with procurement delays of several months. Without EQA, manufacturers

			cannot rigorously assess performance and countries cannot detect laboratory-level failures.
Specimen collection techniques: Recommended approaches for sample collection	A standardised and validated approach is needed to address the technical challenge highlighted above.	High	Create standardised specimen collection SOPs with visual aids and training videos demonstrating optimal swabbing technique for different lesion types, as well as nasopharyngeal swabbing for screening purposes. Include guidance on lesion stage assessment (crusted vs vesicular) and sample adequacy. Disseminate through national laboratory networks and training programmes.
Evaluation centres: Regional evaluation hubs as platforms for diagnostic evaluation	Regional hubs would be able to coordinate rigorous testing of diagnostics in programmatic settings during outbreaks.	Very high	Establish regional evaluation hubs (centres of excellence) with capacity and resources to conduct evaluations on fresh samples during outbreaks, organised by pathogen family
Comparative evaluations: Umbrella studies for multi-product comparisons	Regional hubs would be able to evaluate and compare multiple products to inform implementation decisions and procurement.	High	Conduct comparative evaluations: test multiple RDTs simultaneously in the same population to enable bridging and benchmarking.

Regulatory approvals			
Evaluation criteria: Standardised criteria to guide product evaluation	Multiple regulatory pathways exist for mpox diagnostic approval, each with different requirements and timelines. Confusion about requirements for WHO pre-qualification versus Africa CDC approval and lack of harmonisation creates duplication of effort and delays market entry.	Very high	Establish a joint WHO/Africa CDC/AMA technical working group to align evaluation criteria, particularly for archived vs fresh sample requirements. Establish joint WHO/Africa CDC/AMA regulatory working group to harmonise evidence standards, evaluation protocols and approval criteria. Negotiate mutual recognition agreements allowing one-time submissions recognised by multiple authorities. Develop streamlined 30-day emergency use authorisation pathways for outbreak contexts. Create joint review teams conducting synchronised evaluations to eliminate redundant assessments. For products targeting markets beyond Africa (Europe, Americas), also engage EU regulators (CE-IVDR) and US FDA in mutual reliance discussions. Approximately 50–60% of manufacturers report IVDR as

			a major regulatory hurdle – harmonisation with WHO EUL criteria would reduce duplication.
Mutual recognition criteria: Reliance mechanisms to accelerate approvals	Mutual reliance mechanisms: Enable regulatory authorities to recognise approvals across jurisdictions, reducing duplication.	High	Develop mutual recognition agreements so that products approved by WHO EUL or stringent regulatory authorities can be fast-tracked through Africa CDC and AMA processes.
Emergency use authorisations (EUA): Rapid deployment in outbreak settings	Current regulatory approval processes are slow relative to outbreak dynamics.	High	Create EUA frameworks with clear criteria, transparent review timelines (target: 30 days), and provisional approval mechanisms during active outbreaks. Operationalise 30-day emergency use authorisation pathways with pre-defined evidence packages. Implement rolling reviews where manufacturers can submit data incrementally during product development rather than waiting for complete dossiers. Establish regulatory capacity-building programmes to train NRA staff in expedited review procedures. Create pre-positioned regulatory frameworks allowing immediate activation during PHEICs/PHECS. The AMA and WHO-recognised ML3 regulators should be formally integrated into the EUA pathway as a co-signatory authority. Products granted WHO EUL should receive automatic provisional AMA acceptance pending full dossier review within 90 days or less.
Regulatory guidance for developers: Clarifying regulatory requirements	Developers may be unclear on the requirements of regulators for different categories of product.	High	Publish regulatory guidance documents clarifying data requirements for different test types and use cases. Manufacturers – particularly Chinese companies seeking to enter African and European markets – report that requirements for different product categories (RDT vs near-POC molecular vs lab-based) are poorly communicated, requiring costly and slow dialogue with regulators before submission.

Implementation and integration			
Landscaping: Mapping existing use of mpox diagnostics	Understanding of current capacity and practices will provide insights into development needs	High	Map both: (1) diagnostic capacity (laboratories, platforms, personnel, supply chains across endemic and at-risk countries) and (2) current practices (which tests are being used, by whom, and under what clinical and surveillance scenarios). Combine with policymaker and healthcare worker consultations to define use-case requirements in different settings.

National Essential Diagnostics Lists: Inclusion of mpox diagnostics on National Essential Diagnostics Lists (NEDLs)	NEDLs drive procurement planning, budget allocation and supply chain prioritisation. Most countries have not yet included mpox diagnostics on their NEDLs, resulting in ad hoc procurement during outbreaks, unpredictable supply and stock-outs. Without NEDL inclusion, manufacturers lack demand forecasts necessary for production planning, and ministries of health cannot establish sustainable procurement budgets.	Medium	Advocate for inclusion of mpox diagnostics in NEDLs, with volume guarantees to signal demand to manufacturers. Conduct NEDL advocacy campaigns at national and regional levels demonstrating disease burden, cost-effectiveness and outbreak prevention value. Provide technical assistance to ministries of health for NEDL revision processes. Develop model NEDL language and justification documents. Link NEDL inclusion to pooled procurement mechanisms (e.g. African Medical Supplies Platform), providing volume guarantees that incentivise manufacturer participation. To be effective, NEDL inclusion must be paired with volume forecasts. Based on industry survey data, manufacturers require a minimum sustained demand of 10,000–100,000 tests per year for ≥3 years to justify continued investment. Governments and procurement platforms should publish multi-year demand signals tied to NEDL commitments.
Quality assurance: External Quality Assessment (EQA) programmes for mpox diagnostics	EQA programmes are currently lacking. Reference materials are also not consistently available, particularly during periods of low demand, and procurement delays may extend for several months, limiting timely evaluations and sustained quality assurance activities.	High	Bolster EQA programmes for mpox diagnostics, with at least two proficiency testing rounds per year. Establish and institutionalise new regional EQA programmes by developing standardised EQA panels with characterised positive and negative specimens across different viral loads, clades and specimen types. Build on existing programmes. Create and maintain accessible repositories of reference materials, strengthen regional distribution systems, and appoint regional EQA coordinators to distribute panels and provide feedback.
Human capacity building: Training of healthcare workers	Effective implementation of new diagnostics tools will require training of different categories of healthcare worker.	Medium	Develop training curricula and tools for healthcare workers in different settings (e.g. community health workers for RDTs, laboratory technicians for molecular tests).
Integration with existing diagnostic platforms	There may be opportunities to leverage existing diagnostic technology platforms to reduce implementation barriers.	Medium	Pilot integrated diagnostic networks leveraging existing platforms (TB GenXpert, HIV viral load) to reduce deployment costs.
Procurement: Optimising national procurement processes	Procurement and supply chain: WHO-prequalified products may not be procured by national programmes or international organisations due to cost,	High	Engage pooled procurement mechanisms (AMSP, UNICEF, PAHO) to aggregate national demand and provide volume guarantees. WHO-prequalified products should be prioritised in procurement frameworks. Develop model procurement specifications and cost-effectiveness analysis tools for ministries of health. Preferred

	lack of awareness or preference for established suppliers.		procurement channels per survey: UN agencies (~90%), national tenders (~80%), pooled mechanisms (~60%).

Coordination and engagement			
Coordinating body: Global coordination and monitoring	Coordinated global efforts are needed to accelerate diagnostic development and implementation and to ensure equitable access.	High	Designate a neutral coordinator (e.g. WHO Global Diagnostics Coalition, FIND) to reduce duplication, align initiatives, and ensure critical infrastructure receives sustained investment
Coordination platform: Stakeholder engagement and alignment	Dialogue with developers, regulators and other key stakeholders is needed to promote alignment, provide a forum for dialogue and to shape the work of the global coordinating body.	High	Establish a multi-stakeholder Mpox Diagnostic Coordination Platform (building on existing WHO Global Diagnostics Coalition frameworks) meeting quarterly. Include community and civil society representatives in governance structures to ensure user perspectives inform diagnostic design and deployment.
Existing stakeholder intelligence:	Previous stakeholder engagement has been conducted by Africa CDC (facilitated through the African Society for Laboratory Medicine, ASLM), IPPS 100 Days Mission, and FIND and partners.	High	Extract and synthesise findings from existing stakeholder engagement efforts (Africa CDC, IPPS, FIND databases) to avoid duplication.
Barriers and needs: Identifying developers priority issues/needs	Rather than launching new surveys, the roadmap should leverage existing data and conduct targeted follow-up.	High	Conduct targeted follow-up with manufacturers on current status, barriers and needs, with a focus on actionable feedback rather than extensive surveys. Include small and medium-sized enterprises (SMEs) and academic developers alongside large manufacturers. The FIND industry survey (Feb–Mar 2026, n=30) provides a baseline of manufacturer priorities and commercial thresholds. Rather than launching new surveys, conduct targeted follow-up with the same respondents and expand outreach to non-Chinese manufacturers (currently underrepresented relative to the global manufacturing landscape).

Global/regional public goods and normative guidance			
Diagnostic development support hub	'One-stop shop' to support diagnostic developers.	Very high	Establish a diagnostic development support mechanism providing technical guidance, reference materials, and evaluation support to manufacturers developing POC/RDT products. Establish a global hub with regional nodes (at minimum in Africa and Asia-Pacific, given the geographic distribution of manufacturers). The hub would provide technical guidance, reference antigen/genomic material distribution, evaluation support and regulatory navigation assistance. Model on the WHO FIND partnership for HIV/TB diagnostics.
Target product profiles (TPPs)	TPPs provide key guidance for developers on product requirements. Current mpox diagnostic TPPs need updating.	Very high	Revise the 2023 WHO TPPs to provide clear guidance on different use cases – community-level screening RDTs, near-POC molecular for outbreak investigation, laboratory-based confirmation assays. For each use case, define essential vs preferred specifications for clade differentiation, price thresholds, and minimum sensitivity/specificity anchored to defined clinical use cases.
Reference materials and standards	Reference standards and other materials will facilitate product development and evaluation.	Very high	Create a repository of quantified Mpox antigens and genomic materials for distribution to developers (coordinated by WHO, FIND, and reference laboratories)
Open-platform assays	Locally developed assays compatible with open-platform systems could expand diagnostic coverage and reduce reliance on proprietary technologies; however, uncertainty regarding regulatory pathways for laboratory-developed tests limits their deployment despite available infrastructure.	Medium	Support development and evaluation of locally produced assays compatible with existing open-platform systems and establish clear and affordable regulatory-developed tests.

Regional manufacturing and technology transfer			
Technology transfer	Building regional manufacturing capacity reduces dependency on global supply chains and strengthens preparedness.	High	Support technology transfer initiatives enabling African and other regional manufacturers to produce mpox diagnostics.

Leveraging existing activities	Regional centres already have diagnostic development and production capabilities which could be utilised to enhance regional manufacturing capacity.	High	Leverage existing initiatives: Institut Pasteur de Dakar, Biovac, Afrigen (vaccine/mAb manufacturing platforms that could extend to diagnostics).
Technical assistance	New manufacturers may need support in gaining regulatory approvals.	High	Provide technical assistance and quality assurance to regional manufacturers seeking WHO prequalification.
NRA strengthening	NRA capacity is a prerequisite for sustainable quality assurance and local product approvals.	High	Establish regulatory capacity-building programmes training NRA staff in expedited review procedures. Link to the AMA and WHO regulatory capacity-strengthening frameworks.

Sustainable financing			
Advocacy for funding:	Diagnostics receive substantially less funding compared to vaccines and therapeutics in pandemic preparedness portfolios. Funding is fragmented across multiple donors with different eligibility criteria, reporting requirements and disbursement timelines. This creates inefficiencies, gaps in coverage and sustainability challenges when donor priorities shift. Unlike vaccines, where CEPI provides dedicated financing, diagnostics development lacks a comparable dedicated funding mechanism.	Very high	Advocate for dedicated diagnostic funding streams within pandemic preparedness financing mechanisms (e.g. Pandemic Fund, Global Fund). Establish dedicated financing streams for diagnostic preparedness analogous to CEPI for vaccines. Advocate for diagnostic inclusion in Pandemic Fund proposals and World Bank Health Emergency Preparedness and Response (HEPR) programmes.
Innovative funding mechanisms	Novel funding mechanisms might be needed to incentivise diagnostic development.	High	Explore blended finance models combining public funding for R&D with market-shaping mechanisms (AMCs, volume guarantees). Include explicit price-reduction incentives: subsidies or matched funding for manufacturers achieving production costs ≤$3 ExWorks for RDTs (the preferred price point for ~85% of antigen-based POC developers per the FIND survey). Blended finance models: donor grants for R&D + AMCs for scale-up + results-based financing tied to WHO prequalification milestones. Develop blended finance models combining donor grants, low-interest loans and results-based

			financing. Create multi-year commitments rather than project-based funding to enable sustainable capacity building and manufacturer confidence.
Market assessment and shaping	Limited manufacturer engagement due to unclear market size and episodic demand is a major challenge. Mpox epidemics are unpredictable and episodic, making demand forecasting difficult. Small affected populations (relative to diseases like malaria or TB) result in limited market size. Manufacturers perceive high development costs and regulatory risks with uncertain return on investment. This is especially pronounced for diagnostics compared to vaccines and therapeutics, where advance purchase commitments and stockpiling create more predictable markets.	High	Implement advanced market commitments (AMCs) guaranteeing purchase volumes at specified prices contingent on meeting performance specifications. Establish pooled procurement mechanisms (e.g., African Medical Supplies Platform) aggregating demand across countries. Provide development subsidies and technical assistance to manufacturers, especially those in endemic regions. Facilitate technology transfer agreements enabling regional manufacturing with lower cost structures. AMC design should be anchored to the investment thresholds identified in the FIND industry survey: minimum sustained demand of 10,000–100,000 tests/year for ≥3 years and a maximum shelf life of 12–24 months. AMC volume commitments below these thresholds are unlikely to change manufacturer behaviour,
Pooled procurement	Pooled procurement may improve demand forecasting, incentivise product development and facilitate wider access.	High	Engage with pooled procurement mechanisms (AMSP, PAHO, UNICEF) to signal demand and streamline access.

2. Host–pathogen interactions

New mpox medical countermeasures are required, based on a thorough understanding of **host–MPXV interactions**. However, fundamental gaps remain in understanding the host–virus interactions that determine immune protection, viral evolution, disease severity and transmission.

Poxviruses are complex **double-stranded DNA viruses** that, unusually, replicate exclusively in the cell cytoplasm. During the virus cycle, three types of virus particles are generated, but only two – **mature virus (MV)** and **extracellular virus (EV)** – are infectious. EV particles have an extra outer envelope containing a distinct set of envelope proteins.

MPXV attaches to human cells by recognising **glycosaminoglycans (GAGs)**, present on multiple types of cell. Cell entry involves membrane fusion and is dependent on a multicomponent viral **entry-fusion complex (EFC)** containing 15 viral proteins[22]. Following infection, poxviruses synthesise most of the proteins necessary for their replicative cycle, in a cascade fashion, with each stage dependent on the completion of the previous stage[23].

Once inside the cell, the inner structure (the **core**, containing viral DNA within a nucleocapsid structure) contains all the components required for synthesis of mRNAs necessary for the early (pre-replicative) stage of gene expression. Transcripts are then extruded from virus cores into the cell cytoplasm, where they are directed to cellular ribosomes for the synthesis of **early proteins**, including proteins involved in host immune modulation, viral DNA replication and transcription factors important for late stages of gene expression.

Replication of viral DNA then follows, using viral enzymes. Once new copies of virus genomes start being synthesised, the **post-replicative stage** of gene expression is launched. Virus morphogenesis begins, following the synthesis of proteins necessary for the construction of immature virus particles. Proteolytic processing by viral proteases generates the MV forms, which are the most abundant type of virus particles but remain inside infected cells.

A proportion of MV are directed to the **trans-Golgi**, where they acquire two additional membranes, mediated by several viral proteins. The resulting **wrapped viruses (WV)** are directed to the cytoplasmic membrane, where the most external membrane fuses with the cytoplasmic membrane, externalising a double-envelope virus, the EV. EVs can remain associated with the cellular membrane **(CEVs)** or detach from the cellular surface **(EEVs)**. CEVs are propelled to neighbouring cells through **actin tails** polymerised following a virus-orchestrated hijacking of cellular proteins involved in actin polymerisation. EVs are responsible for long-distance cell infection.

Host responses: MPXV infection triggers a variety of innate immune responses, which are the target of multiple mpox immune evasion mechanisms, for example targeting IFN responses, blocking of viral DNA recognition, inhibiting natural killer cell activity, and triggering the death of dendritic cells.

[22] Lin CS, Li CA, Wang CH et al. Cryo-EM structure of the vaccinia virus entry fusion complex reveals a multicomponent fusion machinery. Sci Adv. 2026;12(3):eaec0254. doi: 10.1126/sciadv.aec0254.
[23] Moss B. Understanding the biology of monkeypox virus to prevent future outbreaks. Nat Microbiol. 2024;9(6):1408-1416. doi: 10.1038/s41564-024-01690-1.

MPXV also triggers both cellular and humoral immune responses. Infection triggers a Th1-type response, which is also suppressed by MPXV, promoting viral persistence. MPXV infection also induces binding and neutralising antibody responses (IgA, IgG and IgM), of variable strength and duration. A variety of immunodominant viral antigens have been identified, including A35R and B6R (EV antigens) and H3L and E8L (MV antigens). Natural protection likely depends on a combination of T-cell and antibody-based responses.

Host responses may also have pathogenic effects[24]. Excessively high levels of a variety of inflammatory mediators could contribute to tissue damage and the severity of disease.

[24] Li H, Huang QZ, Zhang H et al. The landscape of immune response to monkeypox virus. EBioMedicine. 2023;87:104424. doi: 10.1016/j.ebiom.2022.104424.

KNOWLEDGE GAPS:

Subtheme 1: Host factors and immunity			
What host factors and immune mechanisms determine protection against MPXV infection and disease severity?			
Knowledge gap	**Rationale**	**Importance**	**Approach**
Brief description of knowledge gap/research priority	*Statement of why this knowledge gap is important and how closing it would advance MCM development or implementation*	*Very high, high, medium or low*	*Types of study that could address knowledge gap*
Protective immunity			
Protective immunity: What are the key mechanisms that protect against infection and severe disease?	Critical to vaccine design and will facilitate the identification of correlates of protection.	Very high	*See Vaccines section.*
Human genetics: What host genetic traits affect susceptibility, disease severity, immune responses and clinical outcomes?	Multiple host factors are likely to affect responses to MPXV, influencing susceptibility to infection and clinical outcomes. Understanding these factors could help to identify those at risk of adverse outcomes and suggest novel therapeutic strategies.	High	Case–control studies/genome-wide association studies; candidate gene analysis.

Subtheme 2: Viral evolution, clades and pathogenesis			
What are the evolutionary mechanisms and genetic determinants driving MPXV adaptation and clade-specific pathogenesis?			
Knowledge gap	**Rationale**	**Importance**	**Approach**
Antigenic divergence			

Antigenic divergence: How much antigenic divergence exists between circulating MPXV strains?	Will be important to understand the potential for cross-strain protection, informing vaccine design.	Very high	Genomic surveillance.
Impacts on immunity: What impact does antigenic divergence have on breadth or durability of immunity?	As above.	Very high	Integration of genetic characterisation into vaccine/natural history of infection studies.
Implications for vaccines: Are current MVA-based vaccines suboptimal?	Several existing and candidate vaccines are based on MVA, initially developed for protection against smallpox. Antigenic divergence may affect the effectiveness of these vaccines.	High	Animal model, case-control studies.
Mechanisms and rates of MPXV evolution			
Mutational signatures: What mutational signatures, including APOBEC3-like editing, are present in the MPXV genome?	Will provide insights into the routes through which MPXV is being transmitted.	High	Loss-of-function studies, within-host evolution studies.
APOBEC3 editing: What contribution does APOBEC3 editing make to viral diversification and mutational patterns?	Critical for predicting likely viral evolution and potential development of resistance to mpox MCMs.	High	As above.
Evolutionary rates: What are the evolutionary rates for clade I and clade II viruses?	Stability of the MPXV genome will affect the speed at which it might acquire mutations facilitating transmission or affecting disease severity or MCM sensitivity.	High	As above.
Clade-specific genetic determinants			
Gene content: What gene content differences exist between clade I and clade II viruses?	Will provide insights into the underlying causes of the differing properties of clade I and clade II viruses.	Very high	Bioinformatic analuses of gene content.

Immune modulation: Do clade-specific immune-modulatory genes exist?	Will determine whether targeting immune modulation will be effective across clades.	High	Loss-of-function studies.
Antigen recognition: What viral factors affect antigen presentation, cytokine signalling, and innate immune responses?	Will identify key factors underlying any clade-specific immune responses, to inform vaccine design.	High	As above.
Rearrangements: What kinds of structural variation, gene truncations, and gene loss are seen in circulating isolates?	Will reveal the degree to which structural variation drives viral evolution.	High	As above.
Determinants of severe disease			
Viral load: How do viral load dynamics and clinical outcomes vary across clades?	Understanding association between viral load and disease severity will be important to guide clinical care and therapeutics development.	Very high	Case-control studies.
Immune responses: How do immune responses differ between mild versus severe disease?	Critical to guide development of interventions targeting immune responses.	Very high	Transcriptomic, serological cohort studies.
infection routes: How does infection route influence disease progression?	Will provide prognostic information and could inform vaccine and therapeutic design by revealing any route-specific disease mechanisms.	Very high	Animal models; transcriptomic, serological cohort studies.
Systemic dissemination: Does early immune evasion influence systemic dissemination?	May suggest new pathways to target to limit dissemination.	High	As above.
Mechanisms of viral adaptation and immune evasion			
Virulence: What roles do clade-specific genes have in virulence and immune modulation?	Understanding the genetic basis of immune evasion, and of clade-specific differences, will inform therapeutic strategies targeting immune modulation.	High	Animal models; loss-of-function studies.

Immune modulation: How do immune-modulatory proteins differ across clades?	As above.	High	As above.
Gene amplification: What role do gene amplification ('genomic accordion') mechanisms play in adaptation?	As above.	Medium	As above.
Inverted terminal repeats: What are the mechanisms of adaptive variation in inverted terminal repeat regions?	As above.	Medium	As above.
Linking genotype to phenotype			
Mechanisms of infection: How do the mechanisms of infection vary across viral clades?	Genomic surveillance and sequencing studies are generating new data on MPXV genetic variation. Understanding the functional consequences of observed MPXV genetic variation will provide new insights into MPXV virology and inform therapeutics development.	Very high	Animal models; loss-of-function studies.
Tissue tropism: What are the determinants of tissue tropism, viral shedding, and immune modulation?	As above.	High	Animal models; loss-of-function studies.
Evolutionary trade-offs: What are the trade-offs between transmissibility, virulence, and immune evasion?	Understanding the fitness consequences of MPXV genetic variation will reveal factors likely to affect the ability of MPXV variants to spread through human populations.	High	Modelling studies.
Epidemiology: What is the correlation between genomic variation and epidemiological patterns?	As above.	High	Genomic surveillance.
Within-host evolution			

Intra-host evolution: How does MPXV evolve during the course of infection?	MPXV may evolve during infection, potentially affecting sensitivity to immune response mechanisms, virulence or responses to therapeutics. This could be a particular concern in long-lasting infections in immunosuppressed individuals.	Very high	Gain-of-function studies, animal models, transcriptomic studies.
Tissue compartments: How do viral populations differ across tissues such as skin, mucosa, ocular tissue and blood?	As above.	High	Cohort studies; animal models, humanised models.
Escape variants: When and where do potential immune escape variants arise?	As above.	High	Epigenetic, recombinant pseudotyped virus generation, models, neutralising assays.
Transmission bottlenecks: What transmission bottlenecks affect human-to-human spread?	As above.	High	Transcriptomics, humanised models; modelling studies.
Antiviral-driven evolution			
Resistance mutations: When and where do resistance-associated mutations arise in treated patients?	Mutations in the F13L gene are associated with resistance to tecovirimat. When more effective therapeutics are developed, understanding the development of resistance will be important to inform drug stewardship, use of combinations and development of co-treatments targeting resistance mechanisms.	Medium	Genomic surveillance; cohort studies.
Evolutionary pressures: What evolutionary pressures are associated with antiviral use?	As above.	Medium	As above.
Fitness costs: What are the stability and fitness costs of resistance mutations?	As above.	Medium	As above.
Suboptimal dosing: To what degree does suboptimal dosing accelerate viral diversification?	As above.	Medium	As above.

Subtheme 3: Cell and tissue biology of infection			
What are the mechanisms governing MPXV entry, cellular tropism and dissemination?			
Knowledge gap	**Rationale**	**Importance**	**Approach**
Viral entry and host receptors			
Host receptors: What are the molecular mechanisms of MPXV cell entry, and what host receptors mediate attachment and fusion?	An understanding of viral attachment and entry will underpin development of therapeutics to block cell invasion and viral dissemination.	Very high	Pseudotyped viruses, soluble protein assays, surface plasmon resonance studies. Cryo-EM and other structural biology studies.
Virion forms: Do EV (extracellular virion) and MV (mature virion) forms use distinct entry pathways or receptors?	As above.	High	As above.
Tissue dissemination: How do EV- versus MV-specific entry mechanisms shape tissue dissemination?	As above.	High	Animal model studies.
Cell tropism and dissemination			
Early vs late infection: What cellular and tissue tropisms define early versus late stages of infection?	Factors affecting cellular susceptibility to MPXV infection at different stages of infection remain unclear. Cell and tissue vulnerability to infection could influence the course of disease and severity of symptoms.	High	Animal model studies.
Localised vs systemic: What events determine localised infection versus systemic dissemination?	As above.	High	Animal model studies.
Tissue vulnerabilities: Are certain tissues intrinsically more susceptible/resistant to infection due to receptor availability or innate immune response?	As above.	High	Animal model studies. Cell culture/organoid studies.

Localised immunity: Does recruitment of specific immune subsets or tissue-resident cells facilitate or restrict viral spread?	As above.	High	Animal model studies; humanised models.
Severity: Does early infection of specific cell types dictate disease severity?	As above.	High	As above.
Host cell takeover and replication control			
Reprogramming: How does MPXV reprogram host cells to support viral replication?	MPXV has a complex genome of around 200 genes, which code for multiple proteins that interfere with host cell processes. A deeper understanding of the mechanisms of host cell takeover and new virion production will help to identify new therapeutic targets.	Very high	Computational models, gain/loss-of-function studies, transcriptomic/pathway analysis.
Modifying translation: How does the virus regulate host protein synthesis, translation shutdown, or selective translation?	As above.	High	As above.
Heat shock proteins: How do heat shock proteins and the unfolded protein response influence viral replication or host defence?	As above.	High	As above.
Therapeutic targets: What host pathways represent viable therapeutic targets?	As above.	Very high	As above.
Omics technologies: Can integrated transcriptomic and proteomic analyses identify stage-specific host takeover mechanisms?	As above.	High	As above.
Orthopox-specific factors			

Ankyrin-repeat proteins: What are the unique functions of orthopox ankyrin-repeat proteins in manipulating host signalling pathways?	Ankyrin repeat proteins are a large family of virally encoded proteins that play key roles in immune evasion and ubiquitin-mediated degradation of host proteins.	High	Computational models, gain/loss-of-function studies, transcriptomic/pathway analysis.
Host manipulation: How do ankyrin-like proteins alter immune signalling, cell cycle regulation, or apoptosis?	As above.	High	As above.
Virological impact: Are ankyrin proteins determinants of host range or virulence?	As above.	High	As above.

Subtheme 4: Experimental model systems			
How can experimental systems be improved to better model MPXV infection and enhance translation to clinical applications?			
Knowledge gap	**Rationale**	**Importance**	**Approach**
Fidelity of existing model systems			
Long-term effects: How well do current models track viral persistence and long-term sequelae?	Critical for understanding chronic complications and developing long-term treatments.	Medium	Comparative animal model and clinical studies.
Model diversity: Which models are most suitable for addressing specific biological/clinical questions?	Critical for identifying which model to use to address different aspects of MPXV biology, and to inform development of enhanced or standardised models.	Very high	Systematic comparisons of orthopoxvirus infections across model systems.
Viral replication: How do viral replication kinetics and lesion development differ between human infection and murine models?	As above.	High	As above.
Skin tropism: How well do existing mouse models reproduce early skin tropism and localised epithelial dissemination?	As above.	High	As above.

Cell culture: How well do conventional cell culture systems capture early stages of epithelial spread observed in human infection?	Cellular systems are more convenient for research but may not reliably model key aspects of in vivo viral behaviour.	High	As above.
Species-specific immune responses			
Innate immunity: What are the key differences between murine and human innate immune responses to MPXV infection?	Comparative studies will facilitate interpretation of animal data and transferability to human context. Such studies may also provide novel mechanistic insights.	High	As above.
NK cells: How does NK cell biology differ between species?	Essential for translating research findings to human clinical applications	Medium	Benchmarking models against human clinical data, humanised models.
Cytokine responses: What are the key differences in interferon signalling pathways and cytokine responses between species?	As above.	High	Comparative animal model and clinical studies.
Tissue-resident cells: How do tissue-resident immune cell populations differ between murine and human skin?	As above.	Medium	As above.
Species specificity: How do species-specific immune differences influence viral replication and disease progression?	As above.	Medium	As above.

ENABLERS:

Enablers	Rationale	Importance	Approach
Capacity, community tools/resources and other enablers that would accelerate closing of knowledge gaps or overcoming of key barriers	*How these enablers would accelerate development of medical countermeasures*	*Very high, high, medium or low*	*Strategy for developing*
Adaptive immunity			
Prospective cohorts	Prospective cohorts with linked data on clinical severity, viral kinetics, immune profiling (blood, lesion/mucosa where feasible). Important for understanding natural history of infection and deriving correlates of protection	Very high	Map existing cohorts. Identify gaps and potential to standardise analyses across sites.
Standardised immunoassays	Harmonised neutralisation, Fc-function panels, T cell readouts plus WHO-aligned reference standards. Required to facilitate comparisons/syntheses of data from different studies	High	Establish Technical Working Group to compare practice and development community standards.
Standardised live-virus assays and pseudotype/surrogate assays	Use of and comparison to live-virus as gold standard to ensure assay validity	Very high	As above.
Viral evolution			
Genomic surveillance	Global genomic surveillance networks with standardised metadata. Will reveal genetic variants associated with changes in properties of virus, which will need to be functionally analysed.	Very high	Implement standardised pipelines for detecting SNPs, indels, structural variants and recombination. Integrate clinical severity, vaccination history, antiviral use and immune status into genomic datasets.
Longitudinal sampling in immunocompromised individuals	Will provide insights into within-host evolution as a mechanism for viral diversification/ adaptation.	High	Prospective enrollment with emphasis on immunocompromised participants.
Viral isolate repositories	Accessible repositories representing diverse lineages will facilitate comparisons of viral properties, including immune escape.	Very high	Fund a centralised repository with streamlined access and shipping pipelines
Cell and tissue biology of infection			

Reagent library	Needed to provide researchers in all settings with access to standardised reagents/materials (e.g. antibodies, cells, MPXV genes) to ensure equitable research opportunities.	High	Consult to identify community needs and current availability. Develop proposals to establish quality-assured reagent library.
Animal models			
Enhanced translational models for mpox research	Will give insights into MPXV pathobiology not possible with current models. Could be used to develop predictive frameworks linking viral genetic determinants with host-specific disease outcomes. Could be used to identify conserved versus species-specific mechanisms of viral pathogenesis	High	Establish Technical Working Group to map current model use, shortcomings and desirable features.
Integrated model platforms combining human tissue models, animal systems, and computational approaches.	Use of a diversity platforms will provide complementary data and facilitate interplay between experimental and computational platforms.	High	As above.
Standardised model systems for preclinical testing of medical countermeasures.	Use of standardised models will make it easier to compare and aggregate data across studies.		Use above activities to establish consensus on most appropriate translational models.
Integrate model systems with clinical and genomic data	Model systems should be integrated with emerging genomic and clinical datasets to improve translational relevance. Model systems could be used to test hypotheses generated from clinical observations. Clinical metadata could be incorporated into experimental study design	Medium	Ensure close linkage between laboratory and clinical research teams.
Biosafety facilitators			
Enhanced access to BSL-2/3 facilities	Research on live MPXV requires BSL-3 containment facilities, although some MPXV research can be carried out in BSL-2 facilities. Expanding access to such facilities in endemic regions would increase MPXV research capacity.	Medium	Map current capacity for BSL-2/3 studies in endemic areas. If appropriate, develop an investment case to expand BSL-2/3 facilities in such areas.

Novel techniques	Novel techniques applicable in BSL-2 and lower level facilities would enable a wider range of centres to carry out MPXV-related research.	Medium	Establish Technical Working Group to explore potential opportunities to adapt or develop new techniques requiring less stringent containment facilities.

3. Clinical care and infection control

There is little evidence that existing antiviral treatments, developed for smallpox, are of benefit in mpox (see Therapeutics section). Clinical management therefore focuses primarily on supportive care and infection prevention (e.g. isolation).

The evidence base for mpox clinical care and infection prevention and control remains limited. Current WHO recommendations on isolation duration, lesion and wound management, pain control, breastfeeding, sexual-contact restrictions, use of personal protective equipment (PPE), and environmental decontamination are largely extrapolated from other orthopoxviruses (varicella-zoster, herpes simplex), general dermatological practice, or low-certainty data[25].

Major uncertainties persist in key areas, including:

- **Duration of infectiousness and viral shedding** (including pre-symptomatic, asymptomatic and prolonged shedding in immunocompromised individuals).
- Transmission risk via **body fluids** (semen, breastmilk, eye fluid).
- Optimal **diagnostic/triage pathways**, including community-based approaches.
- Optimal **wound-care strategies** across lesion stages and special populations (advanced HIV and immunosuppressed, children, pregnant persons).
- Prevention of **secondary bacterial infections**.
- **Pain management** for mucocutaneous lesions.
- Feasible approaches in **homes and resource-limited** settings.

Standardised lesion classification, outcome measures and patient-reported outcomes are also lacking. There is also no clear-cut guidance on minimising the risk of adverse long-term outcomes such as cutaneous sequelae, and limited data on their impacts on quality of life. Research into the mental and psychosocial wellbeing of people with infections, in convalescence or having been discharged needs to be more explicitly tailored to mpox.

The highest-priority gaps to fill are those that directly inform isolation duration, PPE effectiveness, targeted wound care, pain control and triage/severity scoring in resource-limited settings. An overarching theme for all the knowledge gaps is to ensure that recommendations characterise and differentiate by subclades, sub-populations (age, ethnicity, immunosuppression) and risk settings. Rigorously generated new evidence will feed into global recommendations and development or updating of national clinical guidelines.

[25] https://www.who.int/publications/i/item/B09434

KNOWLEDGE GAPS:

Subtheme 1: Natural history of infection			
How does the course of mpox disease vary by patient type?			
Knowledge gap	**Rationale**	**Importance**	**Approach**
Variability in course of disease			
Natural history: How do host traits affect the natural history of MPXV infection?	Factors such as vaccination history, prior infection, HIV status, immunosuppression and other host factors affect disease presentation, progression and outcomes. An enhanced understanding of variation in the natural history of MPXV infection will inform clinical management and public health guidance.	High	Longitudinal cohort studies.
Triage and severity scoring systems			
Diagnosis and triage: What is the optimal pathway for assessing potential mpox cases?	Limited options are available for point-of-care diagnosis of mpox. Diagnostic algorithms are needed that are applicable to settings with differing access to molecular/laboratory detection methods.	High	

Severity score: How can a standardised severity scoring system support effective triage?	In resource-limited settings, it is important to be able to risk-stratify patients to identify who would most benefit from escalation to inpatient management or higher levels of care. Evidence-based de-escalation protocols are also required.	Very high	Develop severity/triage scoring system for resource-limited settings, using simple bedside variables (e.g. lesion count, lesion type, lesion location, immune status (e.g. HIV, diabetes), mucosal involvement). Pilot score prospectively against hospitalisation outcomes, then set clear cut-offs for referral to higher care.

Subtheme 2: Wound/lesion care			
What is the optimal approach to wound care in different patient populations?			
Knowledge gap	Rationale	Importance	Approach
Optimising wound care for mpox lesions			
Topical care: What is the optimal topical wound care for mpox lesions across disease stages?	Cutaneous and mucosal lesions are the dominant clinical feature of mpox and major drivers of morbidity (pain, secondary infection, scarring, genital complications). In the 2022 global outbreak, most hospitalisations were for severe anorectal pain and bacterial superinfection, and most clinical complications related to mucocutaneous disease rather than systemic viral toxicity. Even so, wound management remains largely experience-based and is not standardised. There are no evidence-based, standardised protocols defining optimal topical wound care	Very high	Pragmatic randomised controlled trials comparing wound care strategies (e.g. moist occlusive dressings vs dry dressings; lesion care with antiseptic vs soap and water alone). Prospective cohort studies evaluating healing time, pain scores, and bacterial superinfection rates. Virologic sampling studies assessing viral load from lesions under different dressing conditions. Implementation research in outpatient and community settings to assess community-centred approaches to lesion care. Inclusion of populations with special vulnerabilities: people living with HIV, pregnant women, children and other immunocompromised populations. Assessment of lesion burden, lesion location and their impacts on total wound care and prognosis. Note: It is important that clade IIb studies carried out in Africa, since factors such as skin types, environment and genetics are

	for mpox lesions across disease stages (macular → papular → vesiculopustular → crusted). Current practice is extrapolated from other viruses (e.g. VZV, HSV) and general dermatologic wound care principles. Closing this gap would: • Reduce preventable complications (cellulitis, abscess, necrosis, scarring). • Potentially reduce onward transmission via optimised lesion care. • Decrease hospitalisation for pain and secondary infection. • Standardise outpatient management in outbreaks and in low-resource settings.		plausible reasons for differences in clade IIb responses in African Americans versus native Africans.
Wound dressings: Do moist vs dry wound dressings affect healing time?	The optimal dressing type for mpox lesions has yet to be confirmed.	High	Randomised controlled trial in endemic country and in different population groups.
Topical agents: Is there a role for topical antiseptics or topical antivirals in wound care?	Topical antiseptics (e.g. chlorhexidine, povidone-iodine) or topical antivirals (e.g. cidofovir) could potentially affect healing times and/or reduce the risk of secondary infections.	High	Randomised controlled trial in endemic country and in different population groups.
Antibiotic use: When should topical vs systemic antibiotics be provided?	Antibiotics are not currently recommended for uncomplicated mpox cases. Topical or systemic antibiotics could be used to treat secondary bacterial infections or, under some circumstances, to prevent such infections.	Medium	

Mucosal lesions: What are best practices for genital, perianal and mucosal lesions?	Genital, perianal and mucosal lesions are typically the most painful and difficult to treat. Specific guidelines are needed for these types of lesion.	High	
Occlusive dressings: What impact do occlusive dressings have on viral shedding?	Occlusive dressings could potentially reduce viral shedding and reduce the risk of MPXV transmission.	Medium	
Viral shedding: How do different wound care approaches alter viral load, environmental contamination, or duration of infectiousness?	Mpox transmission occurs through close skin-to-skin contact and potentially contaminated materials. If certain wound care practices (covering lesions, use of occlusive dressings, cleansing agents) reduce viable viral shedding, this would have direct public health implications.	High	• Longitudinal viral culture and PCR quantification from lesions under different dressing conditions. • Environmental sampling studies. • Household transmission cohort studies based on wound care strategies. • Integration with modelling studies assessing transmission risk.
Pain management for mucocutaneous lesions			
Pain management: What are the most appropriate strategies for management of pain, particularly that associated with anorectal, genital and oropharyngeal lesions?	Anorectal pain is a leading cause of hospitalisation, yet pain management remains entirely experience-based. Evidence-based pain management would: reduce avoidable hospitalisations driven by uncontrolled pain; inform opioid-sparing strategies with relevance to resource-limited settings; enable patient-centred outpatient care; and improve quality of life.	Very high	• Pragmatic randomised controlled trials comparing analgesic regimens by lesion site (anorectal, genital, oral, cutaneous), including topical anaesthetic formulations vs systemic analgesia. • Prospective cohort studies with validated pain-scoring instruments (e.g. NRS, BPI) to characterise pain trajectories across lesion stages. • Evaluation of adjunctive measures (sitz baths, stool softeners, barrier creams) as components of mucosal wound care bundles. • Inclusion of pain outcomes (e.g. pain score) and analgesic use as mandatory endpoints in mpox clinical trials.

Analgesics: How should topical anaesthetics (e.g. lidocaine formulations), sitz baths and systemic analgesics (including opioid-sparing approaches) be used in mpox care?	As above.	High	As above.
Adjunctive interventions: What role do adjunctive interventions (e.g. stool softeners for anorectal disease) have in mpox care?	As above.	High	As above.
Home-based care			
Resource-limited and home isolation settings: What are the most effective wound care approaches in contexts with limited access to supplies, clean water and professional support?	During the 2022 outbreak, isolation at home was the main management approach. In endemic settings wound care must sometimes be delivered by family members or community health workers without access to sterile materials or trained supervision. Without resource-adapted wound care guidance, there is a risk of: inequitable outcomes between well-resourced and low-resource settings; caregiver-acquired infection through unsafe wound handling; and ongoing transmission within households. Guidance that is context-adapted and scalable is essential for outbreak response in high-burden settings.	High	• Implementation research evaluating feasibility and effectiveness of simplified wound care protocols deliverable by patients and caregivers undergoing home-based care. • Household transmission studies assessing infection risk to caregivers under different wound handling and dressing approaches. • Development and validation of low-resource wound care toolkits (e.g. soap and clean water protocols, improvised dressing materials) in partnership with communities in endemic regions. • Community health worker training programmes and telemedicine-supported wound care monitoring for home-isolated patients. • Ethnographic studies on the feasibility of home care in resource-limited settings.
Long-term skin outcomes			

Post-healing sequelae: What are the long-term skin outcomes following mpox infections in different populations?	Scarring was frequently reported during the 2022 outbreak and is a key patient-reported concern, particularly for facial, genital, and perioral lesions. In immunocompromised individuals, deeper tissue involvement increases the risk of hypertrophic or keloidal scarring and functional contracture. The lack of prospective long-term follow-up data means that wound care strategies cannot currently be evaluated for their impact on post-healing skin outcomes. Understanding scarring outcomes would: enable assessment of different wound care interventions on scar burden; inform development of scar prevention and treatment protocols; and support the capture of patient-relevant long-term outcomes in clinical trials.	Medium	• Prospective cohort studies with structured long-term follow-up using validated scar assessment tools (e.g. POSAS), to characterise post-healing skin outcomes. • Randomised trials of topical scar-prevention interventions (e.g. silicone-based preparations, emollients) initiated during the crusting phase, and/or the use of splits in flexural areas of the body to prevent post-infection contractures. • Patient-reported outcome studies capturing psychosocial impact of scarring, including effects on self-image, sexual health, and mental wellbeing. • Inclusion of standardised scar assessment and post-healing follow-up as endpoints in future mpox clinical trials and observational registries. • Dermoscopy impacts in mpox management: comparative study of naked eye examinations of lesion and scar during active, convalescent and long-term sequelae. • Antioxidant adjunctive therapy in mpox management: outcome-based adaptive clinical trial. • Use of dermatology life quality index in assessment of quality of life of mpox patients: acute, convalescent and long-term.
Risk factors: What factors are associated with scarring and other long-term skin outcomes?	Identification of key risk factors could provide valuable prognostic information and support targeting of interventions.	Medium	Prospective long-term cohort studies covering key populations.
Post-healing care: What is the optimal approach to post-healing scar management or cosmetic intervention?	Skin care after infections have resolved could improve long-term outcomes. Cosmetic interventions could provide long-term benefits in severe cases.	Medium	Pragmatic randomised trials in key populations.
Psychosocial consequences: What are the mental health and social implications of scarring,	A deeper understanding of long-term psychosocial impacts could inform post-healing care and provision of mental health support.	Medium	Prospective long-term cohort studies covering key populations.

particularly in facial and genital regions?			

Subtheme 3: Special populations			
What are the optimal care pathways for special populations, including children, pregnant women and people living with HIV?			
Knowledge gap	**Rationale**	**Importance**	**Approach**
Children			
Symptoms: How different are issues such as lesion progression, healing kinetics and complication rates in children?	Limited data exist on lesion progression, healing kinetics and complication rates in children. A deeper understanding would help to optimise wound care for children.	Very high	• Standardised lesion photography, dermoscopy and skin biopsy for histology with healing metrics. • Paediatric-specific observational studies. • Burden and outcome studies in children versus adults.
Treatment: What are the optimal wound care strategies for children at different ages?	As above.	High	Randomised controlled trials of wound care strategies including children at different ages.
Pregnant women			
Symptoms: How different are issues such as lesion progression, healing kinetics and complication rates in pregnant women?	Limited data exist on lesion progression, healing kinetics, and complication rates in pregnant women, with potential implications for optimal wound care.	High	Pregnancy registries including dermatologic outcomes for both mother and child (including comprehensive prospective follow-up: dermatologic, neurological, behavioural, cardiovascular, etc.). Laboratory studies of impacts of infection on placental function.

Treatment: What are the optimal wound care strategies for pregnant women?	As above.	High	Randomised controlled trials of most promising wound care strategies.
Mental health: What are the psychosocial consequences of mpox infections?	Mpox infections may have significant implications for the mental health of pregnant women, particularly if associated with adverse birth outcomes. A deeper understanding of psychological impacts will inform the provision of mental health support.	High	Cohort studies to explore the psychosocial impacts of mpox infections during pregnancy.
People living with HIV			
Symptoms: How do mpox symptoms differ in people living with HIV, including those with inadequately suppressed viral replication?	During the 2022 and current outbreaks, individuals with advanced HIV disease experienced more severe, necrotic and prolonged disease. In such cases, lesions can resemble progressive vaccinia-like pathology, raising distinct wound management challenges.	Very high	Stratified prospective cohort studies by CD4 count and viral suppression status.
Management: How should care be adapted for people living with HIV?	Failure to define best practices in these populations risks: • Higher rates of tissue destruction and scarring. • Longer duration of viral shedding. • Greater hospitalisation burden. • Inequitable outcomes in settings with a high prevalence of HIV.		Randomised controlled trials of most promising wound care strategies.

Antiretroviral timing: What is the risk of IRIS in people living with HIV with mpox not yet on antiretroviral therapy (ART)?	There is a lack of direct evidence comparing rapid vs delayed ART initiation in people living with HIV and mpox. Risks and prevalence of true mpox immune reconstitution inflammatory syndrome (IRIS) are unknown. Existing literature is confounded by lack of consensus case definitions to distinguish IRIS from relapse.	High	RCT comparing early (e.g. immediate) vs delayed (e.g. after 2 weeks) ART initiation with outcome measures being mortality, time to mpox lesion resolution and prevalence of IRIS (utilising a careful case definition to distinguish IRIS from relapse).
Men			
Treatment: What is the best approach for treatment of urogenital infections in men?	MPXV can cause various urogenital manifestations in men, particularly penile lesions. Care pathways need to consider the full psychosocial context of urogenital infections in men including risk of stigmatisation.	High	
Testicular reservoirs: How significant are testicular reservoirs in sustaining MPXV transmission?	There is some evidence that MPXV can replicate in testicular tissue, with viral shedding into seminal fluid creating a transmission risk via sexual intercourse. However, whether this is a major route of MPXV transmission remains unclear.	Medium	

Subtheme 4: Secondary infections			
What is the best approach for preventing and treating secondary/co-infections?			
Knowledge gap	**Rationale**	**Importance**	**Approach**

Incidence: What is the true incidence of bacterial superinfection of mpox lesions in different settings?	Secondary bacterial infections are common, particularly in individuals with extensive lesions or delayed presentation. Under-treatment risks cellulitis, bacteraemia and hospitalisation However, unnecessary antibiotic use risks antimicrobial resistance. Evidence-based criteria would: • Inform antimicrobial stewardship and reduce inappropriate antibiotic prescribing. • Clarify risk stratification. Improve outpatient triage and reduce unnecessary admissions.	High	• Prospective multicentre observational studies documenting rates of culture-confirmed bacterial infection. • Microbiologic characterisation of secondary infections. • Risk modelling studies to identify predictors of bacterial superinfection of mpox skin lesions. • Randomised trials of prophylactic topical therapy in high-risk patients. • Embedded antimicrobial stewardship evaluation during mpox outbreaks.
Predictors: What factors are associated with the risk of secondary infections?	The ability to identify high-risk patients could guide patient care and use of antibiotics.	High	
Prevention: What are the optimal strategies for prevention of secondary infections?	Improved prevention would reduce the need for antibiotics.	High	
Treatment: What factors should guide use of topical or systemic use of antibiotics or conservative management?	A treatment algorithm is needed to guide clinician decision-making.	Medium	
AMR: What impact does antibiotic use in mpox have on antimicrobial resistance?	Over-use of antibiotics in mpox patients would be a contributor to the emergence and spread of antimicrobial resistance.	Medium	

Subtheme 5: Complications			
What are the best approaches for managing ocular and other complications of mpox?			
Knowledge gap	**Rationale**	**Importance**	**Approach**
Ocular complications			
Ocular complications: Is topical trifluridine safe and effective for patients with mpox-related eye pain and/or conjunctivitis/keratitis?	Direct evidence of the effectiveness of trifluridine in mpox-associated eye disease is lacking, and limited to case series in mpox and indirect evidence from herpes keratitis and vaccinia infections.	High	Randomised controlled trials and/or monitored use programmes where feasible. Studies should ideally also look into the impact of mpox affecting the eyelids.
Oropharyngeal complications			
Oropharyngeal care: What is the most appropriate way to assess and manage oropharyngeal manifestations of mpox?	MPXV infections can cause a variety of oropharyngeal symptoms. Oropharyngeal complications need to be systematically described and guidelines developed on assessment, management of oral pain and other symptoms and referral criteria.	Medium	
Oral health settings: What is the most appropriate approach for assessment and management of suspected oropharyngeal cases in dental care?	Evidence-based guidelines are needed to support assessment, triage, referral and infection prevention and control in oral health settings.	Medium	

Subtheme 6: Infection prevention and control			
What are the most effective ways to prevent mpox transmission in clinical and post-clinical settings?			
Knowledge gap	**Rationale**	**Importance**	**Approach**
Duration of infectiousness and viral shedding			
Infectious periods: How long is the infectious period and how does it vary across subpopulations (e.g. for people with immunosuppression), by age, medication, severity of illness and MPXV sub-clade?	Findings will: • Inform targeted PPE/IPC protocols in communities and health and care settings, and clarify the need for and duration of isolation in community and care settings. • Inform isolation duration based on different risk profiles. • Inform PPE use and IPC measures based on severity and risk contact. • Mitigate personal and socioeconomic consequences by optimising isolation periods.	Very high	Multicentre longitudinal prospective platform cohort with nested virology, serology and household transmission sub-studies.
Indirect transmission: What is the risk of indirect transmission and how does it vary by distance?	MPXV can be spread indirectly but the risks associated with indirect pathways of infection are unclear. Additional evidence could guide care practices in facility and home settings and facility management.	High	
Reinfection: What is the risk of reinfection due to waning of antibodies over time?	Existing vaccines offer good protection against mpox but waning antibody responses could place contacts at greater risk of infection.	HIgh	*See Vaccines section.*

Asymptomatic infections: What is the transmission risk associated with asymptomatic infections?	An understanding of such risks would inform infection control strategies and the need for isolation.	HIgh	
Transmission via body fluids			
Vertical transmission: How is the risk of transmission via breastfeeding affected by factors such as severity, neonatal age, maternal antibody protection?	Findings will: • Inform IPC protocols in community and care settings (e.g. breastfeeding, blood banks, transplants). • Inform PPE use (e.g. mouth guards, condoms, facemasks). • Inform guidance on restrictions and duration of restrictions for different clades and risk profiles (e.g. timeframe for refraining from unprotected sexual intercourse and pregnancy following infection). • Inform isolation and breastfeeding guidance to protect neonates/infants. • Ensure benefits outweighs harms.	Very high	Prospective cohort studies**,** retrospective case-control studies and modelling. Multicentre prospective mother–infant cohort with nested virology and immunology studies.
Sexual transmission: What is the risk of transmission via sexual intercourse?	MPXV can be transmitted following sexual contact. The virus has also been detected in semen. Better understanding will inform the sexual and reproductive health advice given to patients.		
Other infectious tissues: What are the other potential routes of person-to-person transmission?	Understanding the risks of non-lesion transmission will inform IPC practices and health advice.	High	

Exposure risk stratification			
Risk categories: What is the relative risk of infection for different types of health worker and community member	Findings will: • Help to identify the need for post-exposure prophylaxis (PEP) in different populations. • Inform the need for and duration of isolation. • Inform guidance on the duration of abstaining from close and sexual contact.	Very high	Healthcare and community cohorts, nested target-trial emulation, prediction modelling.
Post-exposure prophylaxis: How effective is PEP and when should it be initiated?	Vaccination of contacts could help to prevent transmission but immune responses take time to develop. An understanding of immune response kinetics will inform recommendations on use of PEP.	High	*See Vaccines section.*
Effectiveness of personal protective equipment and IPC strategies			
PPE: How effective are different types of PPE?	Different types of PPE (e.g. facemasks, condoms, mouth guards) may offer protection against infection. Additional evidence could be used to inform prevention guidance for sexually active patients.	Very high	Adaptive clinical trial, two-arm RCT comparing different forms of protection.
Isolation: How effective is isolation at reducing transmission and how does this vary by clade and severity of disease?	Findings will inform policy and guidance on need for and duration of isolation in different situations.	Very high	

Home-based care: How effective is home-based care at reducing transmission compared with hospital-based care?	Home-based care of mpox patients is common but may be associated with an increased risk of transmission.		
Environmental contamination and decontamination			
Household/facility practices: How do particle- and aerosol-generating activities (e.g. shaking of linen) affect risk of transmission?	Findings will: • Identify ways to reduce the need for isolation and isolation duration. • Inform targeted and more precise isolation protocols. • Mitigate costs and unintended harm.	Very high	Environmental sampling, environmental pressure and observational transmission studies**;** laboratory suspension/carrier tests; ventilation and air-cleaning studies and experimental field tests.
Disinfectants: How susceptible is MPXV to disinfectants?	Data are needed with respect to issues such as active ingredients, concentrations and contact time, to inform guidance on cleaning practices.	High	As above.
Washing: How susceptible is MPXV to household washing detergents and temperature?	Findings will inform guidance on facility and household washing practices.	High	As above.
Surface contamination: How stable is MPXV in the environment and on surfaces?	Fomites can contribute to mpox transmission. More detailed evidence will provide insights into the duration of viral presence and sustainability in different settings and help to identify environmental decontamination methods to reduce the need for isolation.	High	As above.

Airborne transmission: What is the impact of ventilation or air purifying on risk of transmission?	Although MPXV does not spread efficiently through air, it has been found in respiratory droplets and airborne transmission is a possibility. 'Adequate' levels of ventilation required to prevent airborne transmission need to be defined.	Medium	As above.

ENABLERS:

Enablers	Rationale	Importance	Approach
Capacity, community tools/resources and other enablers that would accelerate closing of knowledge gaps or overcoming of key barriers	*How these enablers would accelerate development of medical countermeasures*	*Very high, high, medium or low*	*Strategy for developing*
Surveillance			
Prospective cohorts	Prospective cohorts with linked data on clinical severity, viral kinetics, immune profiling (blood, lesion/mucosa where feasible). Important for understanding natural history of infection and deriving correlates of protection.	Very high	*See Vaccines section.*
Standardised immunoassays	Harmonised neutralisation, Fc-function panels, T cell readouts plus WHO-aligned reference standards. Required to facilitate comparisons/syntheses of data from different studies.	High	*See Vaccines section.*
Clinical trial infrastructure			
Research and trial protocols	Pre-positioned harmonised research and trial protocols in strategic areas and diverse settings. Needed for timely implementation of clinical research during outbreaks.	Very high	
Coordination and collaboration, research networks, partnerships	Will facilitate harmonisation of protocols, effective implementation, and inclusion in trials.	Very high	
Outcome measures			
Standardised lesion classification and clinical severity scoring	The absence of an international standardised lesion classification and severity scoring makes it difficult to compare outcomes across studies, assess treatment response, or evaluate wound care interventions. A harmonised lesion staging system and severity index would allow consistent outcome measures for clinical trials and observational	Very high	• Develop a consensus mpox lesion staging system through expert consultation. • Adapt existing dermatologic scoring frameworks used for varicella, HSV and dermatologic infections or validate existing scores like the mpox severity score more broadly.

	studies evaluating supportive care strategies and antivirals. Standardised metrics would also enable pooling of data across outbreaks and geographic regions, accelerating evidence generation for best practices in lesion management.		• Validate scoring systems in prospective outbreak cohorts. • Integrate standardised documentation into WHO clinical case report forms.
Harmonised outcome measures for lesion healing	Clinical trials evaluating antivirals, vaccines and supportive care require consistent endpoints. Currently, studies use heterogeneous measures such as time to crusting, time to lesion resolution, or viral clearance. Standardised wound healing endpoints would allow direct comparison across trials and facilitate meta-analyses.	Very high	• Define consensus endpoints such as time to cessation of new lesion formation. time to full re-epithelialisation, duration of pain, rate of secondary infection. • Develop validated patient-reported outcome measures (PROMs) for lesion-related symptoms. • Integrate endpoints into clinical trial protocols.
Integration of patient-reported outcomes	Pain, functional limitation and psychosocial distress are major drivers of morbidity in mpox but are poorly captured in clinical research. Incorporating patient-reported outcomes would provide a more complete assessment of treatment effectiveness and help prioritise supportive care interventions.	Medium	• Develop mpox-specific PROMs focused on pain, mobility, hygiene and quality of life. • Integrate electronic symptom tracking tools into clinical studies. • Validate instruments across diverse populations and settings.

4. Vaccines

Mpox vaccination is an essential public health intervention, both in historically endemic regions and in non-endemic regions following the expansion of transmission[26]. Currently available mpox vaccines are vaccinia-based orthopoxvirus vaccines targeting smallpox, while newer products designed to improve safety while retaining cross-protection against mpox are in development. These vaccines provide broad protection against orthopoxviruses, including MPXV.

Third-generation live-attenuated vaccinia-based vaccines – **MVA-BN** (non-replicating in humans) and **LC16m8** (minimally replicating in humans) – are the first-line vaccines recommended for preventing mpox[27]. In Africa, 16 countries have received mpox vaccines, and 15 have initiated mpox vaccination for outbreak response since late 2024.

Access remains constrained by high vaccine cost (MVA-BN), limited commercial access (LC16m8), and uneven country readiness linked to policy, regulatory, logistical challenges and other health system priorities. Increasing global supply or the number of approved vaccines may improve availability, but access will continue to depend on affordability, regulatory readiness, delivery capacity, and health system preparedness in endemic countries.

Other licensed smallpox vaccines, such as **ACAM2000** (replication-competent live virus) and **OrthopoxVac** (live-attenuated, minimally replicating), are also approved for mpox as they offer cross-protection against orthopoxviruses in general. Potential issues include their safety in populations such as people living with HIV with immune suppression and pregnant women and children, the feasibility of their administration, and their acceptability to the community. Use of replication-competent vaccinia vaccines must consider the potential for adverse events such as myocarditis/pericarditis, inadvertent inoculation and contact transmission, and the need for associated risk mitigation.

Progress has been made recently in mpox vaccine development and vaccination strategies. In particular, the safety profile of MVA-BN is increasingly well established, alternative dosing strategies including intradermal administration are emerging as feasible dose-sparing approaches, and clinical trials are generating data on vaccine use in groups such as pregnant women, adolescents and children. However, important evidence gaps remain, particularly regarding:

- **Durability of protection** and booster requirements.
- Vaccine effectiveness in **clade I endemic settings**.
- Potential for interference following **coadministration of other vaccines**, particularly childhood vaccines.
- **Operational delivery** in outbreak and endemic contexts.
- Behavioural and health-system factors that influence **acceptability, trust, uptake and equitable access**.

[26] https://www.who.int/publications/i/item/who-wer-9934-429-456

[27] Shafaati M, Forghani S, Shahsavand Davoudi A et al. Current advances and challenges in mpox vaccine development: a global landscape. Ther Adv Vaccines Immunother. 2025;13:25151355251314339. doi: 10.1177/25151355251314339. eCollection 2025.

These remaining gaps are particularly pronounced in resource-constrained endemic settings, where implementation challenges and health system limitations, constrained laboratory and clinical research capacity, and insufficient implementation and social science research not only affect programme delivery, but also hinder the generation of context-specific evidence needed to strengthen the field and inform vaccination policy and practice[28].

The mpox vaccine development pipeline is reasonably well stocked, with several candidates (mostly mRNA vaccines) in clinical trials and multiple others at advanced stages of pre-clinical development. Clarity is required on the regulatory pathway(s) for new vaccines if traditional phase III efficacy trials are not feasible. These may vary by vaccine platform.

[28] Furst R, Antonio E, de Swart M, et al. Gaps in the global health research landscape for mpox: an analysis of research activities and existing evidence. *BMC medicine* 2025; **23**(1): 522.

Table 1. Orthopox vaccines used or recommended for mpox*

Status	Generic name (and brand), regulatory authorisation and WHO guidance	Platform	Description	Dosage and route	Cold chain requirements
Licensed mpox vaccines					
Licensed mpox vaccines (i.e. with full market authorisation in one or more jurisdictions)	**ACAM2000**** SAGE guidance for orthopoxvirus vaccination in mpox outbreaks	Live vaccinia virus, non-attenuated replication-competent vaccine	Second generation (derived from Dryvax vaccine)	Single-dose/percutaneous with multiple puncture technique using bifurcated needle	+2 to +8°C, up to 30 days after reconstitution (per label)
	MVA-BN (JYNNEOS® ; INVAMUNE® or; INVANEX®) SAGE recommended and WHO prequalified	Live vaccinia virus, highly attenuated non-replicating vaccine	Third generation	Two doses (4 weeks apart); subcutaneous, with intradermal administration (fractional dose) authorised under FDA Emergency Use Authorisation for adults ≥18 years in high-risk populations during vaccine shortages	Frozen storage required for liquid frozen presentation; once thawed and stored at +2 to +8°C, shelf life is limited and should follow the specifications outlined in the locally approved product label
	LC16m8 SAGE recommended and WHO Emergency Use Listed (EUL)	Live vaccinia virus, attenuated minimally replicating	Third generation	Single-dose/percutaneous with multiple puncture technique using bifurcated needle; produces a localised cutaneous reaction (take)	Frozen, up to ten years; +2 to +8°C, up to 2 years
	Vacdelta6 (OrthopoxVac®)	Live vaccinia virus, attenuated minimally replicating vaccinia virus (VACΔ6)	Fourth generation (as defined by attenuation through gene deletion)	Single-dose/intradermal injection with needle and syringe	+2°C to +8°C up to 2 months

*Regulatory indications for these vaccines may differ by jurisdiction. Several orthopoxvirus vaccines are licensed primarily for smallpox prevention but have been used for mpox based on cross-protection and WHO/SAGE guidance. Use for mpox may therefore be off-label depending on national regulatory frameworks.

**Because of the higher risk of adverse events, ACAM2000 has had limited use in mpox outbreak vaccination responses, where safer non-replicating vaccines such as MVA-BN have generally been preferred.

Mpox vaccine landscape

Vaccine	Developer	Description	Advanced pre-clinical	Phase I	Phase II	Phase III	Licensed*	Plans/comments
MVA-BN	Bavarian Nordic	Attenuated (non-replicating)						
LC16m8	KM Biologics	Attenuated (minimally replicating)						
ACAM2000	Emergent Product Development Gaithersburg	Non-attenuated						
VACΔ6/ OrthopoxVac	Vector Institute	Attenuated (minimally replicating)						
GEO-MVA	GeoVax	Attenuated (non-replicating)				Planned launch H2 2026		Following EMA accelerated approval pathway, proceeding directly to a phase III immunobridging trial
MVA-SIBP	Shanghai Institute of Biological Products	Attenuated (non-replicating)						https://clinicaltrials.gov/study/NCT07253675
mRNA-1769	Moderna	mRNA vaccine						https://trials.modernatx.com/study/?id=mRNA-1769-P101
BNT166a	BioNTech	mRNA vaccine						https://clinicaltrials.biontech.com/trials/BNT166-01
BNT166c	BioNTech	mRNA vaccine						Not progressed to phase II
Ospavir	FSUE NPO Microgen	Inactivated						
NTV	Beijing Institute of Biological Products	Attenuated IND approved						
TNX-801	Tonix Pharmaceuticals	Single-dose, horsepox-based IND approved						Phase I planned for Kenya with KEMRI https://ir.tonixpharma.com/news-events/press-releases/detail/1594/tonix-pharmaceuticals-presented-data-on-tnx-801-mpox

Mpox vaccine	Chongqing Zhifei Biological Products	Attenuated						
Monkeypox mRNA vaccine	Ab&B Bio	mRNA vaccine IND						https://en.abbbio.com/news/71.html

Pre-IND vaccine candidates (as of September 2026):

- ≥ nine mRNA vaccine candidates.
- ≥ one DNA vaccine candidates.
- ≥ one subunit vaccine candidates.

KNOWLEDGE GAPS:

Subtheme 1: Protective immunity			
What host responses confer protective immunity and which can be used as correlates of protection?			
Knowledge gap	**Rationale**	**Importance**	**Approach**
Brief description of knowledge gap/research priority	*Statement of why this knowledge gap is important and how closing it would advance MCM development or implementation*	*Very high, high, medium or low*	*Types of study that could address knowledge gap*
Natural immunity			
Correlates of protection: What immune responses correlate with protection against mpox infection, severe disease and transmission?	No validated immune correlates exist. Identification of correlates of protection and protective thresholds will accelerate vaccine development and enable immunobridging.	Very high	Use prospective human immunology studies embedded in vaccine effectiveness cohorts, outbreak investigations and household contact studies, with sampling before and after vaccination and, where possible, before and after exposure or breakthrough infection. Compare people who remain uninfected or develop mild disease with those who develop infection or severe outcomes. Use validated animal models; where ethically and scientifically appropriate, controlled human infection model (CHIM) studies using minimally replicating vaccinia virus strains could be considered. Apply harmonised and validated assays and test the association between binding and neutralising antibodies (NAbs) and protection. If possible, determine a threshold/level (e.g. NAb titre) associated with protection. As exploratory outcomes, test Fc-effector functions, memory B cells, antigen-specific CD4+ and CD8+ T cell responses, and systems immunology to identify broader immune signatures associated with protection. These analyses should explicitly consider population-specific differences, including people living with HIV, pregnant people, immunocompromised individuals, adolescents, infants and populations with prior smallpox vaccination or prior mpox exposure.
Humoral versus cellular immunity: What are the relative contributions of antibodies, $CD4^+$ and $CD8^+$ T cells, NK cells,	Orthopoxvirus immunity is multi-faceted but ill-defined. Knowledge will inform vaccine design and evaluation.	High	Use mechanistic studies that profile humoral and cellular immunity in parallel in vaccinated, previously infected and breakthrough cases. Combine neutralisation, binding antibody, Fc-mediated functional assays (ADCC, ADCP, complement deposition), memory B cell assays, intracellular cytokine staining/ELISpot for CD4+ and CD8+ T cells, and NK cell activation assays. In

and Fc-mediated functions in protection?			selected animal models, use passive-transfer and depletion experiments where feasible to dissect the relative contribution of antibodies, T cell subsets, and innate effector functions.
Antigen-specific targets: Which MPXV antigens and epitopes are targeted by protective immune responses?	Effective immunity may require a coordinated humoral and cellular response against multiple antigens rather than a single dominant epitope. The most important antibody targets are MV proteins (such as L1, H3, D8, A27) and EV proteins (especially B5 and A33), which are highly conserved across orthopoxviruses and enable cross-protection from smallpox vaccines. $CD4^+$ and $CD8^+$ T cell responses against structural and early viral proteins contribute to protection. No single MPXV antigen has yet been clearly identified as independently predictive of protective immunity in humans.	High	Map protective targets using antigen-level and epitope-level studies across vaccinated and convalescent populations. This should include recombinant MPXV antigen panels spanning mature virion and enveloped virion proteins, peptide pools for T cell epitope mapping, B cell antigen mapping, and functional antibody assays linked to specific antigens. Integrate these data with sequence conservation analyses across clades and orthopoxviruses to prioritise antigen combinations that drive breadth, cross-reactivity and protective immunity.
Mucosal immunity: What role do mucosal immune responses play in preventing infection/ transmission?	MPXV transmission frequently occurs through mucosal exposure. Understanding the role of IgA and tissue-resident T cells could guide vaccine development.	Medium	Undertake dedicated mucosal immunology studies in cohorts at risk of sexual and other mucosal exposure, with longitudinal sampling from blood and relevant mucosal compartments where feasible (for example genital, rectal, oral, or lesion-associated samples). Measure mucosal IgA and IgG, antibody functionality and tissue-homing or tissue-resident T cell features, and relate these to viral detection, shedding and infection risk. Comparative evaluation of systemic versus mucosal vaccination strategies could be considered.

Infection- versus vaccine-induced immunity: What immune signatures distinguish prior infection from vaccination?	This is important for separating vaccine-induced from infection-induced immunity, improving interpretation of immunogenicity data, and enabling serological tools to contribute more meaningfully to surveillance and epidemiology, particularly in populations with prior smallpox vaccination or mixed exposure histories.	Medium	Use comparative immunoprofiling of vaccinated-only, infected-only, and hybrid-immunity cohorts to identify signatures that discriminate infection from vaccination. Approaches may include serology against infection-enriched antigens, fine specificity mapping of antibody responses, T cell specificity and profiling, or the use of combined humoral and cellular features. Validate existing findings and test tools in real-world surveillance and vaccine-evaluation settings.

Subtheme 2: Optimising protection			
How well do existing vaccines protect different populations and what are the requirements for new products?			
Knowledge gap	**Rationale**	**Importance**	**Approach**
Vaccine-induced immunity			
Clade I: How effective are existing vaccines against clade I viruses, particularly clade Ib?	Limited field data are available on the effectiveness of existing vaccines against clade Ib MPXV.	Very high	
Durability: How durable are immune responses following infection or vaccination?	Durability of protection and immune memory are incompletely defined. Knowledge will inform vaccine regimens and long-term protection.	High	Establish longitudinal cohorts with follow-up after vaccination and after natural infection to define vaccine efficacy and durability of immune memory. Sample beyond early peak responses to medium- and longer-term timepoints and include assessment of recall capacity after re-exposure or revaccination. Measurements should include binding and neutralising and non-neutralising

			antibody functions, memory B cells, long-lived plasma cells, and antigen-specific CD4+ and CD8+ T cell memory subsets.
Vaccine platform: How do vaccine platforms affect the magnitude, quality, breadth and durability of immune responses?	Different platforms (mRNA, viral vector, protein-adjuvant, live-attenuated) induce distinct immune profiles. Understanding these differences is critical for selecting optimal platforms, designing new vaccines and improving durability and breadth.	Medium	Perform head-to-head or harmonised comparative studies of leading platforms, including MVA-based vaccines, mRNA, protein-adjuvant, and other approaches. Evaluate not only peak immunogenicity but also breadth, durability, boosting potential, mucosal responses where relevant, and performance in priority populations. Comparative analyses should use a common assay toolbox and should link immunogenicity profiles to practical considerations such as dose sparing, manufacturability, cold chain, and suitability for outbreak response.
Prior exposure: How does prior smallpox/mpox vaccination or prior mpox infection influence protection and immunity to MPXV?	Prior orthopoxvirus immunity, including vaccine-induced, infection-induced and hybrid immunity, influences protection and vaccine responses, and should be considered when interpreting immune responses and vaccine efficacy following vaccination.	High	Conduct comparative cohort studies stratified by prior smallpox vaccination, prior mpox vaccination, documented prior mpox infection, and orthopoxvirus-naive status. Assess baseline immunity, vaccine take, recall responses, cross-reactivity and boosting after vaccination or exposure. These studies should include older adults with historical smallpox vaccination, recently vaccinated populations, and people with hybrid immunity to determine how pre-existing orthopoxvirus immunity shapes the magnitude, specificity and durability of responses. Carefully consider bias when including different age groups.
Homologous/ heterologous dosing: What impact does heterologous vaccine dosing have on protective efficacy?	There is a need to assess heterologous vaccination strategies to maximise safety, effectiveness and impact of available products (e.g. prime boost strategy with one dose of a highly attenuated vaccine followed by a dose of a likely more effective replicating vaccine).	Medium	

Dose-sparing: What is the impact of fractional dosing (single-dose MVA-BN) on vaccine effectiveness?	Mpox vaccine supply is limited. MVA-BN is a two-dose vaccine but a single-dose dose-sparing strategy could enable more people to be vaccinated and make vaccination more cost-effective. Clinical studies indicate that single-dose MVA-BN offers good protection but confirmatory effectiveness data are needed.	High	Prospective cohorts; test-negative designs, outbreak-based cohort studies, case-control or case-cohort studies.
Target groups: How does immunogenicity and safety of different vaccines vary between target populations?	There is a need to better identify which vaccines can be used in which populations and under which conditions given their respective characteristics.	High	Clinical trials in relevant populations.
Vaccine safety			
Real-world evidence: What is the incidence and spectrum of serious and non-serious adverse events following mpox vaccination in real-world use?	Study populations may not reflect field conditions, co-morbidities or programmatic delivery contexts. For replicating vaccines such as LC16m8, large-scale active safety surveillance will be essential to detect rare adverse events and maintain public confidence	Very high	Active safety cohort studies; sentinel site surveillance.

	during outbreak vaccination programmes.		
Special populations: What is the safety profile of mpox vaccines in people living with HIV (PLHIV), pregnant women and children?	These populations are under-represented in the data available to date; additional data would inform policy guidance for different populations in different contexts, including historically endemic settings.	High	Prospective observational cohorts; pregnancy exposure registries; phase IV trial; retrospective effectiveness analyses.
Co-administration: Can mpox vaccines be safely co-administered with other routinely used vaccines?	Administration of mpox vaccine could potentially interfere with immune responses to other vaccines, including those routinely used in childhood.	High	Immunogenicity studies with co-administered vaccines in the appropriate age groups.
Alternative vaccine-delivery strategies			
Antigen delivery: Are alternative delivery strategies (e.g. microarray patches) a viable option for mpox vaccination?	Microarray patches are a needle-free vaccine technology with multiple advantages, including easier logistics and pain-free administration. Several technology platforms are in development. Intradermal delivery has advantages, including the potential for reduced doses, but requires specialist training. Needle-free intradermal	High	Support development of microarray patches for mpox vaccination. Conduct acceptability and usability studies with potential users and recipients to assess likely demand. Carry out economic analyses to assess potential cost barriers. Assess potential implementation and economic impact of needle-free intradermal vaccine dispensers.

	vaccine dispensers have been developed that are easier to use.		

Subtheme 3: Population benefits of vaccination			
What is the population-level impact of currently used vaccines?			
Knowledge gap	**Rationale**	**Importance**	**Approach**
Real-world data analysis			
Effectiveness: What is the real-world effectiveness of mpox vaccines in preventing transmission and clinically relevant mpox outcomes?	Robust effectiveness data are available for MVA-BN, including single- and two-dose regimens and intradermal administration. However, data remain limited for clade I endemic settings, duration of protection, transmission, effectiveness in specific populations and exposure contexts, and the effectiveness of post-exposure prophylaxis strategies, including vaccination alone versus vaccination combined with antiviral treatment.	High	Prospective cohorts; test-negative designs, outbreak-based cohort studies, case-control or case-cohort studies.
Exposure intensity: How does exposure intensity affect vaccine effectiveness?	Risk of infection and immune challenge differs substantially by exposure intensity (household, sexual networks,	Medium	Stratified effectiveness analyses within cohorts during epidemic.

	healthcare exposure); pooled effectiveness estimates may mask important heterogeneity.		
Durability of protection: How does durability of protection differ between primary vaccination and booster doses, by vaccine platform, dose regimen, or population group?	Although antibody kinetics and immune memory are increasingly well described for some vaccines, the duration of clinical protection and how it varies by vaccine platform and dosing regimen remain unclear. In particular, immune responses and durability of protection following booster doses may differ from those observed after primary vaccination, as booster doses may induce higher and more sustained immune responses. Early antibody decline after primary vaccination may not necessarily reflect long-term durability of protection, as antibody decay often slows over time.	High	Longitudinal immunogenicity and effectiveness cohort studies; breakthrough infection studies; comparative effectiveness studies of different dosing regimens; and randomised or non-randomised trials comparing primary and booster vaccination strategies.

Subtheme 4: Outbreak control
What impact do vaccines have on transmission and outbreak dynamics?

Knowledge gap	Rationale	Importance	Approach
Viral shedding: How does vaccination affect viral load, duration of viral shedding and shedding at key anatomical sites (e.g. skin lesions, mucosa)?	Even partial reduction in shedding could substantially reduce onward transmission; however, current data are sparse and inconsistent.	Medium	Prospective cohort studies, viral load and duration analyses stratified by vaccination status, and, where ethically and scientifically appropriate, potentially controlled human infection model (CHIM) studies using minimally replicating orthopoxvirus strains (e.g. modified ACAM2000 or LC16m8) to better characterise vaccine effects on infection dynamics and transmission potential.
Outbreak dynamics: How does vaccination influence outbreak size, duration and reproduction number (R_e)?	Policymakers require evidence on the extent to which vaccination strategies can meaningfully alter outbreak trajectories, not just protect vaccinated individuals.	High	Mathematical modelling using field data; quasi-experimental studies comparing vaccinated vs unvaccinated clusters.
Indirect protection: Does vaccination provide indirect protection to unvaccinated individuals in highly vaccinated clusters?	Indirect protection could amplify public health impact.	High	Cluster-based observational studies, household transmission studies, modelling using field transmission data to estimate indirect protection.
Secondary transmission: Does vaccination reduce secondary attack rates among close contacts?	Understanding secondary transmission among close contacts (household, sexual networks, healthcare settings) is critical for evaluating vaccination strategies.	High	Contact tracing analyses; randomised controlled trials of post-exposure vaccination in households.
Changing mpox epidemiology: What role has vaccination played in the decline in mpox case numbers in Africa?	The reasons for the recent decline/stabilisation of mpox cases in Africa remain unclear. Understanding the contribution of vaccination and other factors will help	High	Epidemiological studies combining surveillance and vaccination data to assess factors influencing transmission trends.

	guide future vaccination strategies.		

Subtheme 5: Programme design and implementation			
How can the design and management of mpox vaccination programmes and campaigns be optimised?			
Knowledge gap	**Rationale**	**Importance**	**Approach**
Vaccine programme design			
Optimising deployment: How can mpox vaccines be optimally deployed to maximise protection for different population groups under varying outbreak response scenarios?	Deployment strategies will depend on a range of factors including the populations affected, vaccine properties, vaccination schedules and the stage of an outbreak (different vaccination strategies may be required depending on the timing and stage of the outbreak, including short-term reactive vaccination strategies for outbreak control and longer-term preventive strategies for outbreak prevention in endemic areas). Planning for vaccine deployment also requires better understanding of vaccine demand under different outbreak scenarios, short- and long-term supply projections, and the	Very high	Comparative effectiveness studies; randomised or non-randomised studies of homologous and heterologous vaccination strategies; immunogenicity studies; implementation research; and mathematical modelling to evaluate optimal vaccination strategies under different outbreak scenarios, including different timing, demand and supply scenarios. Cost-effectiveness analyses to assess health economic impact of vaccination (cost per DALY/QALY averted, cost per case/hospitalisation prevented as well as long-term population impact).

	flexibility to adapt vaccine allocation across countries and populations as epidemiological situations evolve.		
Booster policy: How should information on durability of protection be used to guide booster policy?	This information is essential to inform booster dose policies, dose-sparing strategies, and long-term vaccination strategies.	Very high	
Logistics and delivery			
Acceptability: How acceptable is delivery of multiple puncture-based vaccines in outbreak settings?	While large-scale use of LC16m8 in Africa since 2025 has demonstrated programmatic feasibility, published data documenting safety, effectiveness and acceptability in outbreak settings remain limited. However, ongoing studies, including a test-negative case-control study in the DRC, are expected to provide additional evidence. Further documentation of programmatic experience will be important for informing future use of this vaccine.	High	Test-negative case-control studies; prospective safety and effectiveness studies; qualitative acceptability studies; and implementation research embedded in outbreak vaccination campaigns and/or other research studies.
Cold chain: How do cold-chain requirements differ	Different platforms require different logistics and	High	

across platforms in real-world settings?	monitoring. The extensive experience acquired in Africa since 2024 should be documented.		
Wastage: What factors drive vaccine wastage during mpox outbreaks?	Vaccine wastage can have a significant impact on the cost-effectiveness of vaccination programmes.	Medium	Logistics and wastage studies.
Health workforce readiness and training			
Training: What training is required for safe administration of mpox vaccines	Intradermal techniques require specialised skills, while multiple puncture technique can be used by trained community volunteers.	High	Training needs assessment for different products for different purposes in different contexts.
Supervision: What supervision models best support quality and safety?	Poor supervisory practices can have safety implications and undermine public trust.	Medium	Mixed-methods approaches.
Programme monitoring and data systems			
Data integration: How can vaccination data be integrated into routine surveillance systems?	Without linkage, effectiveness and safety cannot be routinely measured.	High	Digital system adaptation studies.
Coverage indicators: What are the best indicators for monitoring equity and reach during outbreaks?	Campaign monitoring needs to consider both overall coverage in target populations and delivery to underserved and hard-to-reach groups.	High	Monitoring framework development.

Vaccine safety and pharmacovigilance			
Background AESI rates: What are the background incidence rates of adverse events of special interest (AESI) for mpox vaccines?	Assessment of safety issues will depend on an understanding of background incidence rates in mpox-affected regions. Interpretation of data from pregnancy registries will require information on background incidence rates of adverse birth outcomes.	High	Epidemiological studies in mpox-affected regions, particularly around sites hosting clinical trials.
PV capacity: How robust are national and subnational AEFI systems to detect, report, and respond to mpox vaccine safety signals?	Weak pharmacovigilance systems can delay detection of rare adverse events and undermine public trust.	Very high	Health system readiness assessments; mixed-methods evaluations of AEFI reporting completeness and timeliness; consistent use of vaccine-specific AESI list.
Active surveillance: Is active safety surveillance feasible during mpox outbreaks and mass vaccination campaigns?	Replicating vaccines and emergency use contexts require rapid, proactive safety monitoring.	Very high	Pilot active surveillance studies; implementation research embedded in vaccination campaigns

Vaccine confidence and community engagement			
Vaccine acceptability: What are the best ways to ensure vaccine acceptability and optimise take-up among target populations?	Perceptions of benefit, risk and necessity directly influence vaccine uptake. Multiple other behavioural and social drivers can also affect take-up.	Very high	*See Social and Behavioural Sciences section.*

ENABLERS

Enabler	Rationale	Importance	Approach
Capacity, community tools/resources and other enablers that would accelerate closing of knowledge gaps or overcoming of key barriers	*How these enablers would accelerate development of medical countermeasures*	*Very high, high, medium or low*	*Strategy for developing*
Immune responses/real-world evidence			
Existing clinical cohorts and studies with potential for integrated immunology	Existing vaccine, key population and natural history cohorts offer major opportunities for immunological studies, but these are often underused because sampling is limited and PBMC or longitudinal specimens are not routinely collected. Better integration of immunology into these studies could accelerate understanding of vaccine responses, prior immunity and breakthrough infection, and facilitate identification of correlates of protection.	High	Embed standard immunology sampling into existing and planned vaccine, observational and natural history studies; prioritise collection of PBMC alongside serum/plasma where feasible; align sampling timepoints with key clinical and virological endpoints.
Established immunology assay platforms and laboratory capacity	Existing assay platforms and laboratory expertise developed for other infectious diseases could be leveraged for mpox immunology, with greater coordination and harmonisation improving comparability across sites and studies.	High	Leverage existing platforms through harmonised SOPs, shared reagents and cross-site validation, and support laboratory networks generating comparable humoral and cellular immunogenicity data.
Vaccination status data linkage	Limited ability to link vaccination data with laboratory-confirmed mpox outcomes is a missed opportunity to collect real-world evidence on vaccine effectiveness.	High	Enhance linkage of vaccination status and laboratory data.
COPs/new vaccine development			
Target product profile (TPP)/preferred product characteristics (PPC)	TPPs and PPCs provide developers with clarity on the essential and preferred characteristics of vaccine products, de-risking development and ensuring that products meet user needs.	Very high	Convene a Technical Working Group to work with WHO/PDVAC on updating of the mpox vaccine TPP and potentially producing a PPC.

Reference standards and shared control reagents	Early reference sera and comparator materials already support assay calibration and benchmarking. Expanding these into shared reference standards would improve comparability across studies and laboratories.	High	Develop and share reference standards including well-characterised serum panels, standardised panels of viruses, shared antigen and peptide reagents, and monoclonal antibodies for assay benchmarking and inter-laboratory comparison.
Standardised assays	Validation of neutralising antibody titre (or other biomarkers) will require consistent use of standardised assays.	High	Convene a Technical Working Group to coordinate efforts to establish and validate a correlate of protection suitable for regulatory decision-making.
Vaccine candidate evaluation			
Standardised trial endpoints	Consistency in trial endpoint use will facilitate data aggregation and cross-trial comparisons.	Very high	Convene a Technical Working Group to develop a consensus on preferred trial endpoints.
Pre-reviewed protocol	A pre-reviewed clinical trial protocol would enable a clinical trial to be rapidly launched during an outbreak.	Very high	Collective development of a trial protocol through R&D Blueprint mechanisms.
Clinical trial platform	A clinical trial platform/network in a state of readiness is needed to host clinical studies in the event of an outbreak.	Very high	Capacity strengthening of potential trial sites.
Ethics and regulatory preparedness for mpox vaccine research	Delays or inconsistencies can hinder safety studies, post-approval research and adaptive trials.	Very high	Process evaluations of fast-track trial approvals.
Outbreak response			
National leadership and stewardship	Strong stewardship is required to align vaccination, surveillance, safety monitoring and research agendas during outbreaks.	High	Comparative case studies of national mpox responses.
Stakeholder coordination and governance	Fragmented coordination slows response and safety-signal management.	High	Governance mapping: comparative outbreak coordination studies.
AEFI and vaccine safety systems	Weak safety systems can undermine trust and delay detection of rare adverse events.	High	Health system readiness assessments; pilot active safety surveillance studies.
Effective programmatic deployment			

Health workforce readiness and training	Mpox vaccines require specialised skills that affect safety, confidence and effectiveness	High	Training needs assessments; pre-/post-training evaluations; supervision model studies.
Programme monitoring and data systems	Without robust monitoring, programme effectiveness and equity cannot be assessed.	High	Indicator development studies: evaluation of digital and paper-based monitoring systems.
Efficient supply chain and stock management	The effectiveness and timeliness of campaigns will depend on good vaccine logistics. There is limited evidence on stock forecasting, wastage and cold-chain performance for mpox vaccine.	High	Operational research on logistics, wastage, and cold-chain monitoring.
Integration with routine immunisation and outbreak response systems	Mpox vaccination relies on routine and emergency systems not originally designed for this pathogen.	High	Health system integration studies.
Vaccine confidence			
Public confidence in mpox vaccines and vaccine programmes	Effectiveness of vaccination campaigns will depend on take up by target groups.	Very high	Effective community engagement and risk communication (RCCE). *See Social and Behavioural Science section.*
Regulatory mechanisms			
Harmonised, streamlined regulatory mechanisms	Robust but rapid approvals are required to ensure timely access to new vaccine products.	High	Close engagement with national regulatory authorities and regional bodies. Consider as part of wider R&D Blueprint programme.
Clarity on regulatory evidence requirements	Developers need clear guidance on regulators' evidence needs, including acceptance of immunogenicity data, and how these might vary by vaccine use case and vaccine platform.	High	Work with WHO, regulators, developers and other stakeholders to ensure that evidence needs are clearly defined and communicated.
Access/manufacturing			
Vaccine availability (routine)	Vaccine supply is currently insufficient to meet global demand. Vaccine allocations are managed by the multi-party Access and Allocation Mechanism (AAM).	High	Liaise with the AAM and other stakeholders to explore key factors affecting vaccine availability and potential solutions.

Vaccine availability (outbreaks)	Effective control of mpox outbreaks will require not only adequate vaccine supply but also timely and equitable access to meet national demands.	Very high	Assess likely needs in different geographies according to current epidemiological trends and potential outbreak scenarios. Identify barriers to vaccine access, procurement and deployment; develop recommendations to improve equitable access during future outbreaks.
Sustainable financing	Reliable domestic or other funding will be required to ensure optimal use of mpox vaccines.	High	Map potential sources of funding and identify funding gaps. Consider the need for an active market-monitoring and market-shaping initiative to ensure availability.
Regional vaccine manufacturing	National and regional vaccine security will be strengthened.	Medium	Integrate within wider vaccine security/manufacturing initiatives.
Capacity-building			
Local research leadership and capacity	Locally led research improves relevance, ethics and long-term capacity. Vaccinology capacity is limited in high-burden settings, particularly sub-Saharan Africa.	High	Partnership and authorship analyses. Promotion of equitable research partnerships (South–North and South–South) and networks to build research capacity in high-burden settings.

5. Therapeutics

Therapeutic options for mpox and other orthopoxvirus infections remain limited. Antiviral agents developed for smallpox, such as **tecovirimat**, **cidofovir** and **brincidofovir,** have shown activity against orthopoxviruses *in vitro* and in animal models, and some have been used during recent mpox outbreaks. However, high-quality randomised clinical trials failed to demonstrate clinical efficacy with tecovirimat[29] [30]. The ongoing MOSA trial will provide data on brincidofovir[31].

Pipeline: Only a small number of derivatives of licensed therapeutics and mpox-specific candidates are in clinical development, with others at preclinical stages[32] [33]. The activity spectrum of candidate therapeutics varies widely, from narrow-spectrum orthopoxvirus-specific agents to broad-spectrum antivirals. A variety of **monoclonal antibody** therapeutics are in preclinical development.

Potential targets: Poxviruses are complex double-stranded DNA viruses that replicate exclusively in the cell cytoplasm. During the virus cycle, three types of virus particles are generated, but only two – mature virus (MV) and extracellular virus (EV) – are infectious. EV particles have an extra outer envelope containing a distinct set of envelope proteins. Cell entry depends on a multicomponent viral entry-fusion complex (EFC) containing 15 viral proteins. Poxviruses replicate autonomously within the host cell, synthesising most of the proteins necessary to complete their replicative cycle.

Five main groups of proteins are potential targets: the enzyme(s) required for viral genome replication (**viral DNA polymerase**), components of the **EFC**, viral enzymes involved in **gene expression** (e.g. polyA polymerase, CAP enzyme, RNA polymerase subunits), proteins involved in **virus morphogenesis**, and those involved in **EV formation and virus release** from cells (e.g. F13, B5, A36, A33).

There is also potential to screen existing drugs for activity against MPXV to assess **repurposing opportunities**[34], or to assess compounds whose development has been halted. **Host-directed therapies** may be an alternative or complementary approach, to inhibit viral replication or to interfere with inflammatory responses driving severe disease.

WHO developed a **target product profile (TPP)** for mpox antiviral therapeutics in 2022[35]. This now needs to be reviewed and updated as necessary, and a complementary **target compound profile** developed to provide guidance to developers on the preferred biochemical and biophysical characteristics of candidate therapeutics.

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Challenges: Key issues for mpox therapeutic development include:

- **Animal models** are not fully predictive of human efficacy.
- The use of antivirals as monotherapies raises the risk of accelerated **resistance** to newly developed therapeutics; monoclonal antibodies are also potentially vulnerable to viral evolution, highlighting the need to target highly conserved structures.
- **Limited access** to drugs in low- and middle-income countries, regulatory uncertainties and the challenges of running high-quality clinical trials during outbreaks limit the ability to collect clinical efficacy and safety data on candidate therapeutics.
- **Capacity for clinical research studies** is low in key geographies such as sub-Saharan Africa.
- Several **key populations** (e.g. children, women, people living with HIV) are typically excluded from pivotal clinical trials, leading to important data gaps.

Mpox therapeutics pipeline

Agent	Developer	Description	Pre-clinical	Phase I	Phase II	Phase III	Licensed*	Plans/comments
ANTIVIRALS								
Tecovirimat	SIGA Technologies	Inhibits VP37 envelope wrapping protein, blocking cellular transmission Oral					No longer recommended for mpox by either the US FDA or the EMA	No evidence of significant efficacy against mpox in major trials
Cidofovir	Gilead	Inhibits viral DNA polymerase Injectable/topical					Off-label for mpox	Significant safety concerns
Brincidofovir		Cidofovir pro-drug Oral Targets DNA-dependent DNA polymerase						Being evaluated in the MOSA trial
NV387	Nanoviricides	Host-mimetic nanomedicine platform that targets heparan sulfate proteoglycans						Mpox orphan drug designation application filed February 2026
BSY001	Beijing Beishengyan Pharmaceutical Technology	Target not disclosed						
NIOCH-14	Federal Budgetary Research Institution-State Research Center of Virology and Biotechnology VECTOR	Tecovirimat analogue						
ASC10	Ascletis Pharma	IND approved; targets viral polymerase; phase I completed (SARS-CoV-2)						
UMM-766	USAMRIID/Merck	Early lead						

		Targets DNA-dependent RNA polymerase						
ST357/TTP-018	Siga Technologies	Early lead Targets mRNA poly-A polymerase						
TTP-6171	Siga Technologies	Early lead Targets I7L-proteinase						
CMLDBU6128 and derivatives	Boston University/US CDC	Early lead Targets DNA-dependent RNA polymerase						
HPMPDAP (diaminopurine)	Academy of the Sciences of the Czech Republic	Early lead Targets DNA polymerase						
7-deaza analogues of S-adenosyl methionine (e.g. TO427)	Academy of the Sciences of the Czech Republic	Early lead Targets RNA 2'-O methyltransferase (VP39)						
5-iodo-2-deoxyuridine	Rega Institute for Medical Research	Early lead Targets DNA polymerase						
NPP-669	University of Michigan/TSRL, Inc.	Cidofovir pro-drug; broad-spectrum antiviral						
LAVR-289	NeoVirTech SAS, France	Brincidofovir analogue; broad-spectrum antiviral						
FC-6407	University of Pennsylvania	Targets the D4 DNA processivity factor						
Based on categorisation used by the Intrepid Alliance. Multiple other compounds with activity against MPXV have been identified through in vitro or in silico studies.								
BIOLOGICS								
Vaccinia immune globulin IV (VIGIV)								
Anti-A35 (EV35 series)		MAbs from convalescent sera						

A138 (M1R), B026 (B6R): dual-target antibody cocktails		Antibody discovery and structural validation is complete. These cocktails target both MV and EV so they are strong targets. NHP data are limited.						
A29 + B6: Bispecific antibodies		Discovery and in vitro potency complete. Still in early to mid-preclinical phase.						
E8 (D8 ortholog)-targeting monoclonal antibodies		Discovery and in vitro neutralization complete. Still in mid-preclinical phase. Best used in combination therapy strategies.						
Broadly neutralizing orthopoxvirus antibodies targeting MV and EV		Still at discovery stage. Animal studies limited and candidate selection not finalised.						
Antibody cocktails (MV and EV)								
H2 anti-A35: Plant-derived mAbs		Expression platform validated and functional activity demonstrated; still in early preclinical phase. GMP manufacturing not yet established.						
LNP-mRNA platform	Beijing Institute of Microbiology and Epidemiology	Ab cocktail delivered via mRNA route						

HOST-DIRECTED								
Pidotimod, thymosin		Generic 'immune boosters' with the potential to counteract MPXV immune evasion						Limited data on use for mpox
PA104	US CDC	One of a set of Retro-1 analogues targeting retrograde transport pathway						

*For smallpox and mpox and in some territories.

KNOWLEDGE GAPS:

Subtheme 1: Licensed antivirals			
Is there a role for tecovirimat or other existing antivirals in mpox treatment?			
Knowledge gaps	**Rationale**	**Importance**	**Approach**
Brief description of knowledge gap/research priority	*Statement of why this knowledge gap is important and how closing it would advance MCM development or implementation*	*Very high, high, medium or low*	*Types of study that could address knowledge gap*
Tecovirimat: Is there a role for tecovirimat in mpox treatment?	Trial data have so far been disappointing, providing little justification for further trials. However, limited data are available for some populations (e.g. people living with HIV).	Low	Tecovirimat's clinical impact might be higher if given early in infection. The ability to reliably diagnose mpox soon after infection might justify further trials, for example in high-risk groups and in combination with other antivirals.
Is tecovirimat safe and effective in pregnant/lactating women?	Tecovirimat is considered safe for use in this group, but limited human data are available. Given the lack of evidence of efficacy, further studies are a low priority but existing data could be collated.	Low	Collation of existing data.
Would combination antiviral treatments including tecovirimat be more effective than antivirals given as monotherapy?	Complementary/synergistic effects might improve efficacy. Combinations would reduce the risk of resistance development.	Very high	In vitro studies to identify optimal combinations/doses, followed by an RCT in an endemic setting.
Would combination antiviral treatments reduce the likelihood of on-treatment resistance emerging?	Groups such as immunosuppressed patients might benefit from antiviral treatment but antiviral monotherapy could drive the development of resistance.	High	RCT in an endemic setting.

Cidofovir: Is there a role for use of cidofovir in cases of severe disease (or more generally)?	Animal studies suggest that cidofovir might be active against MPXV but toxicity is a concern. The requirement for IV administration is also an issue. Given other options, further clinical studies are not justified.	Low	NA
Could cidofovir be used as a topical agent?	Topical use could alleviate toxicity concerns and be a cheap and more accessible treatment, especially for patients with ocular symptoms and milder cutaneous disease; limited human data exist.	High (severe eye symptoms) Medium (prevention of ocular disease and for skin lesions)	RCT in an endemic setting.
Brincidofovir: Is there a role for brincidofovir, as a monotherapy or in combination with tecovirimat?	Brincidofovir is less toxic than cidofovir but limited human data exist on mpox treatment. Adverse events remain a concern; benefits may outweigh the risks in cases of severe disease.	High/very high	MOSA study will provide key field efficacy data and influence future research directions.

Subtheme 2: Antivirals in development			
What other antivirals in development have potential as mpox treatments?			
Knowledge gaps	**Rationale**	**Importance**	**Approach**
Preclinical candidates			
Targets: What are the most promising targets of mpox therapeutics?	Some targets may offer greater prospects of success; alternatively, neglected targets may also exist.	Very high	Systematic assessment of actual and potential targets.
Resistance mechanisms: What viral escape mechanisms exist for common MPXV targets?	A knowledge of resistance mechanisms could inform drug development or design of inhibitors.	High	In vitro studies.
Shelved assets: Do compounds whose activity has been halted have activity against MPXV?	Existing data will exist for shelved assets, potentially accelerating development	High	In silico assessment of potential assets followed by experimental studies.
Combinations: Do combinations provide synergistic effects or protect against development of resistance?	Therapeutics targeting different pathways may have synergistic impacts and reduce the likelihood of resistance	Very high	In vitro studies with candidate therapeutics in combination.
Repurposing opportunities			
Anti-parasite drugs: Could antimalarials or other anti-parasite drugs be repurposed for mpox?	In vitro studies suggest that various anti-parasite drugs (e.g. atovaquone, niclosamide) have an inhibitory effect on MPXV.	Very high	Demonstration of activity in cell-based assays as well as in animal models at doses that are achievable/tolerable in humans.
Existing antivirals: Could existing compounds with known antiviral activity (e.g. ribavirin) be repurposed for mpox?	In vitro and in silico studies suggest that existing antivirals may have activity against MPXV.	Very high	Standardised assessments to generate data on activity and toxicity from cell-based assays and in animal models.
Validation: How can candidates for repurposing identified through in silico screens be rapidly evaluated/triaged?	In silico screening has identified multiple repurposing opportunities. In general, there is limited experimental evidence for biological activity and no mechanism to prioritise for further evaluation.	Very high	Standardised assessments to generate data on activity and toxicity from cell-based assays and in animal models.

Subtheme 3: Host-directed therapies			
Do immune modulators or other host-directed therapies have potential as mpox treatments?			
Knowledge gaps	**Rationale**	**Importance**	**Approach**
Inflammatory responses: Does hyperinflammation play a key role in mpox patients with severe manifestations?	An understanding of the role of hyperinflammation would indicate whether anti-inflammatory drugs, alone or in combination with antivirals, could contribute to treatment of severe mpox cases.	High	Further studies of the mechanisms of hyperinflammation and contribution to pathology; evaluation of interventions in experimental models.
IRIS: What are the risks associated with ART initiation in people living with HIV?	Initiation of antiretroviral therapy (ART) in people living HIV could trigger immune reconstitution inflammatory syndrome (IRIS), paradoxical worsening of symptoms due to a reinvigorated immune system. Risk of IRIS could indicate a need for corticosteroid treatment.	High	Monitoring of people living with HIV on ART, including CD4 count and viral load measurements if IRIS is suspected. Evaluate corticosteroid use if warranted.
Immunomodulation: Do existing 'immune boosters', alone or in combination with antiviral therapeutics, improve clinical outcomes?	Mpox utilises several immune evasion mechanisms. Existing immunomodulatory agents could potentially target these mechanisms and boost immune responses to mpox virus.	Medium	Animal model studies, followed by clinical trials if appropriate.
Immune evasion: Would new agents targeting specific mpox immune evasion mechanisms deliver clinical benefits?	Deeper understanding of mpox–host interactions could suggest new therapeutic targets and support development of host-targeting therapeutics.	Medium	*See Host–Pathogen Interactions section.*

Subtheme 4: Biologics			
What monoclonal antibodies or other biologics in development have potential as mpox treatments?			
Knowledge gaps	**Rationale**	**Importance**	**Approach**
Vaccinia immune globulin intravenous (VIGIV): Is VIGIV a viable option for treatment of patients with significant immunodeficiency?	Some positive human data exist; could provide an option for people living with HIV. However, VIGIV demonstrates variable potency and is not mpox-specific.	Very high	Mpox-specific small animal studies. Non-human primate trials.
Monoclonal antibody (mAb) therapeutics			
Feasibility: Are monoclonal antibodies a feasible approach for treating and preventing mpox infections?	Multiple therapeutic mAbs are in pre-clinical development. Protective in mice; some data available from NHPs. No clinical data yet available. Given their likely high cost, the equity implications of mAb therapeutics need to be considered.	High	NHP studies, followed by IND-enabling studies and clinical trials.

Subtheme 5: Treatments for mpox complications			
Do existing or developmental therapeutics have potential in treatment of ocular or other clinical manifestations of mpox?			
Knowledge gaps	**Rationale**	**Importance**	**Approach**
Treatment of ocular or other manifestations: Can any existing or developmental therapeutics be safely used to treat mpox complications?	MPXV infections can have a variety of clinical manifestations, including ocular and neurological complications, which may require targeted treatment.	High	Evaluation in appropriate animal models before clinical trials.
Tecovirimat, cidofovir, brincidofovir	Only cidofovir is currently available as a topical formulation; limited clinical data are available.	Medium	Synthesis of existing data on topical cidofovir; further evaluation in appropriate animal models before clinical trials, if warranted.
Trifluridine eye drops	Limited clinical data: Some anecdotal evidence exists of positive impacts on	High	Synthesis of existing data; evaluation in appropriate animal models before clinical trials, if warranted.

	ocular complications. Corneal toxicity apparent with extended use.		
Ganciclovir gel	Limited clinical data: Some case reports of use as a topical treatment for ocular mpox.	Medium	As above.
Cidofovir 0.5% eye drops	Case report of successful treatment of long-standing mpox keratitis.	High	As above.
Povidone-iodine	Used as a topical antiseptic. Limited data are available for mpox use; considered a supportive measure rather than a curative agent.	Medium	As above.
Vaccinia immune globulin IV (VIGIV)	Used to treat vaccinia complications. Limited data exist relating to ocular application; possible side effects in animal models.	Low	As above.

Subtheme 6: Post-exposure prophylaxis

Could directly acting antiretrovirals prevent MPXV infection in close contacts of mpox patients?

Knowledge gaps	Rationale	Importance	Approach
Existing antivirals: Are existing directly acting antivirals affective at preventing MPXV infection?	Vaccination is recommended to prevent infection and/or reduce the severity of symptoms in close contacts of mpox patients. Currently available antivirals are not well suited to PEP due to lack of efficacy or safety concerns.	Low	NA.
Novel antivirals: Might more efficacious antivirals be appropriate for mpox PEP?	Chemoprophylaxis could be envisaged when more effective antivirals with improved safety profiles are developed.	High	Randomised controlled trials of new therapeutics with appropriate efficacy and safety profiles.

ENABLERS:

Enablers	Rationale	Importance	Approach
Capacity, community tools/resources and other enablers that would accelerate closing of knowledge gaps or overcoming of key barriers	*How these enablers would accelerate development of medical countermeasures*	*Very high, high, medium or low*	*Strategy for developing enablers*
Global guidance			
Updated target product profiles (TPPs)	TPPs provide guidance to researchers and developers, to support the development of tools with the greatest clinical utility, including in low-resource settings.	Very high	*A Technical Working Group should be established to review and update current mpox therapeutics TPP.*
Target compound profile (TCP)	Provides a consensus view of the most desirable biochemical and biophysical properties of candidate mpox therapeutics, to guide candidate selection and structural optimisation.	Very high	*A Technical Working Group should be established to develop an mpox therapeutics TCP.*
Drug discovery			
Target identification	A deeper understanding of host–pathogen interactions and the mpox virus life cycle in animal models and human cells will highlight the most promising targets for mpox therapeutics.	Very high	*See Host–Pathogen Interactions section.*
Genomic surveillance data	Active surveillance is needed to monitor viral evolution and to identify new viral variants that affect treatment effectiveness. The Africa CDC Mpox Research Consortium assists in the coordination of studies, standardising	Very high	*See Epidemiology and Diagnostics sections.*

	data collection and promoting local research.		
Systematic benchmarking of antiviral activity	Evaluation of in vitro antiviral activity using a panel of viruses (and strains) and a standardised assay to benchmark antiviral activity for current and emerging compounds, to inform prioritisation of candidates for further evaluation/optimisation.	Very high	Identify a network of laboratories to propose which viruses and strains, susceptible cells and assay readouts are optimal for a systematic evaluation of multiple antivirals. Secondary or follow-on assays could be utilised in certain instances; however, the main purpose would be to create a feasible and practical approach to benchmark antiviral activity for known and future antiviral compounds. This approach has utility not only for compounds targeting mpox/other poxviruses but could be part of an overall strategy for all clinical phase antivirals across priority viral families.
Systematic drug-repurposing evaluation	As safety data already exist, repurposing drugs may save time and financial resources.	Very high	High-throughput screening using cell culture, using vaccinia virus as a surrogate model. Potentially focus on existing broad-spectrum antiviral drugs/compounds (although broad-spectrum activity may be associated with a greater risk of off-target effects).
Screening strategies	High-throughput screening can identify new leads for therapeutic development.	High	Coordinate screening of available libraries, with standardised evaluation criteria.
Structure-based drug discovery	Increasing availability of molecular structures increases opportunities for structure-based drug discovery.	High	Establish a pipeline for evaluation of structure-based candidates against standardised criteria.
Advanced *in silico* modelling	AI and other digital tools have potential at multiple stages of target identification, drug discovery and development.	Medium	Explore potential to apply emerging AI tools to accelerate mpox therapeutic development.
Mitigating the risk of resistance	The use of a single antiviral and for prolonged time may lead to the selection of resistant viruses.	Very high	Early testing of combination treatments with different targets.
***In vivo* evaluation**			
Robust experimental models	Multiple animal models are used to study MPXV disease mechanisms and to test interventions. Refined animal models (including monkey, rabbit and dog	Very high	*A Technical Working Group should be established to review existing models and develop recommendations on optimal models and potential refinements.*

	models) are needed, as well as innovative models such as organoids and organ-on-chip systems.		
Clinical evaluation			
Endpoint standardisation	Standardised endpoints enable key clinical outcomes to be assessed and treatment data compared across trials.	Very high	*A Technical Working Group should be convened and carry out a community consultation to identify a consensus set of clinical and virological endpoints for treatment trials and recommended assays.*
Enhanced clinical trial networks, expanded access/IND protocols	The use of protocols that allow access to available antiviral treatments while simultaneously collecting safety and efficacy data will be beneficial	Very high	*A Technical Working Group should explore potential to create adaptive trial platforms to test therapeutics as they become available, including combinations wherever possible.*
Decentralised diagnostic tools	The development of near-care diagnostics can accelerate patient diagnosis and recruitment into trials. Regional manufacturing capacity will need to be developed to provide these tools in a cost-effective manner.	Very high	*See Diagnostics section*
Regional capacity strengthening	Multiple aspects of R&D capacity need strengthening in high-burden countries, including clinical trial infrastructure. The Partnership to Accelerate Mpox Testing and Sequencing in Africa (PAMTA) aims to strengthen local manufacturing and diagnosis capabilities in endemic regions.	Very high	Map existing capacity for mpox clinical research in high-burden settings and use to identify key capacity-development needs.
Regulatory approvals			*To be considered at the cross-family level. Identify any mpox-specific considerations.*
Approvals pathway	Clarity is needed on regulatory pathway and evidence needs for regulators and policymakers in high-burden settings.		
Regulatory alignment	Consistency in approach between regulators will accelerate approvals and access to therapeutics. Reliance mechanisms may also expedite regulatory review.		

Manufacturing and access			*To be considered at the cross-family level. Identify any mpox-specific considerations.*
Equitable access	Access to mpox therapeutics should be according to public health need. Financial barriers may limit access to therapeutics in high-burden settings.		Routes to access should be considered early in the development pathway. Access should be part of R&D funding agreements. Financial accessibility should be an integral part of the TPP.
Sustainable financing	Financing needs to be available to ensure timely access to therapeutics in a public health crisis and in low-resource endemic settings.		Dependent on the availability of an effective therapeutic.
Procurement	Pooled procurement mechanisms can ensure that supply and demand are balanced, and may deliver cost savings.		Dependent on the availability of an effective therapeutic.
Stockpiles	A stockpile may be required to ensure rapid access to therapeutics in a public health crisis.		May be particularly important for any therapeutics used off-label.
Manufacturing	A diversified manufacturing base is necessary to ensure reliable supplies and regional health security.		Public funding should include consideration of technology transfer to facilitate manufacturing in high-burden countries/regions. Liaise with regional/global bodies to develop a strategy to facilitate regional mpox therapeutic manufacturing capacity, within wider MCM security strategies.

6. Social and behavioural science

Mpox outbreaks are **biosocial events**. They are shaped by wider political and economic factors and do not affect populations equally. Effective control and optimal deployment of medical countermeasures is therefore dependent on an understanding of **contextual factors** shaping the dynamics of mpox outbreaks, as well as **pre-existing vulnerabilities**.

Mpox social and behavioural science (SBS) research has grown since the 2022 global outbreak; however, critical gaps remain. This is especially evident in sub-Saharan Africa. A 2025 review identified 50 SBS studies conducted in African settings; most were cross-sectional, small-scale or embedded in larger clinical trials[36]. The majority of SBS studies (70–80%) are rapid assessments designed to inform immediate responses, while only a minority, around 20–30%, are more in-depth or based on methodologically rigorous or theoretically informed research.

Specifically, there is limited evidence on how communities in Africa, particularly groups such as gay and bisexual men who have sex with men and other key populations, understand and respond to mpox countermeasures, particularly vaccines. This includes perceptions of vaccine safety, concerns regarding side effects, and public understanding of regulatory processes, such as emergency or conditional approvals.

Understanding social and behavioural dimensions is essential for the effective development and implementation of mpox medical countermeasures (MCMs) and for implementing public health measures in ways that avoid harm to communities. Factors such as risk perception, trust in institutions, stigma, misinformation and structural barriers to accessing care strongly influence whether individuals seek testing, engage with treatment, or accept vaccination[37]. Engagement and communication approaches that clearly explain evolving evidence, safety monitoring and eligibility criteria are critical to sustaining public trust during countermeasure rollout.

Furthermore, a similar range of issues affect willingness to **participate in research**, including during outbreaks. Mechanisms to evaluate medical countermeasures will struggle to deliver evidence if communities are unwilling to participate. Furthermore, research raises issues such as randomisation and placebo controls that require careful engagement with target populations.

In summary, there is a need for sustainable investment in SBS research before, during and after public health emergencies to create a robust body of evidence on outbreak preparedness and response[38]. This section builds on the extensive sociobehavioural science evidence base as well as experience from implementation of social, behavioural and biomedical interventions for other infectious diseases such as HIV, Ebola and TB from the African context. Mpox-specific evidence has been generated through use of umbrella qualitative protocols, including one developed for rapid deployment during mpox outbreaks in African settings[39].

[36] Duclos D, Schmidt-Sane M, Macgregor H. A review of the social and behavioural science research landscape for mpox in African settings. 2026. Social Science in Humanitarian Action Platform (SSHAP). www.doi.org/10.19088/SSHAP.2026.002

[37] WHO. Advancing social and behavioural research for a community-centred public health response to mpox: meeting report, Kinshasa, Democratic Republic of the Congo, 27-28 November 2024. 2025. Geneva: WHO

[38] WHO. Interim guidance on social and behavioural research for the mpox public health response. 2025. Geneva: WHO

[39] https://www.protocols.io/view/an-umbrella-protocol-for-qualitative-research-in-i-36wgqpee3vk5/v1

KNOWLEDGE GAPS:

Subtheme 1: Risk communication, community engagement (RCCE) and trust			
What are the best ways to build sustainable trust and leverage community-led mobilisation to improve the uptake of medical countermeasures (MCMs) and promote behavioural changes across diverse population groups?			
Knowledge gaps	**Rationale**	**Importance**	**Approach**
Brief description of knowledge gap/research priority	*Statement of why this knowledge gap is important and how closing it would advance MCM development or implementation*	*Very high, high, medium or low*	*Types of study that could address knowledge gap*
Community perceptions: How do communities perceive and respond to the roll-out of medical countermeasures, including experimental or conditionally approved interventions, during mpox outbreaks?	Public understanding of conditional approvals, safety monitoring, and improved guidance may influence trust, acceptance and adherence to vaccination and treatment strategies during emergency responses.	High	Rapid ethnographic surveys; mixed-methods social and behavioural research (e.g. qualitative interviews, focus group discussions). Communication strategy assessments during and after emergency roll-out of MCMs.
Changing perceptions: How do public understanding, risk perception, stigma and preventive behaviours evolve over time, both during and between outbreaks?	Public attitudes, perceptions and behaviours are not static but evolve over time due to many influences. Tracking such changes over time will help to identify significant social influences and inform community engagement, risk communication and vaccination strategies.	High	As above, with longitudinal dimension.

Participatory approaches: How can participatory approaches and/or community-led civil society engagement be institutionalised in emergency contexts to inform risk communication and community engagement?	Communities have local and contextual knowledge, which is critical to implementing public health responses that are acceptable, relevant and feasible. Top-down messaging is less likely to be successful if it ignores local power structures.	Very high	Participatory action research; ethnographic studies on local leadership; comparative case studies of community-led vs state-led interventions; citizen ethnography.
Communication with children: What are the most effective strategies for communicating about mpox risks with children and their caregivers and engaging on their wider needs?	Children are disproportionately affected by mpox. Beyond the physical toll, they may experience profound loss and grief during and after an outbreak, further complicating recovery. However, there is a critical lack of evidence on how to communicate zoonotic risk and hygiene messages to children effectively without causing additional trauma or exacerbating social stigma.	Very high	Developmental psychology-based messaging trials, participatory workshops, the use of photovoice, focus groups with parents/paediatricians, and evaluation of child-friendly visual aids and storytelling. Different approaches will be required with different age groups.
Infodemiology: How do information ecosystems drive misinformation, and which interventions are most effective at countering misinformation?	Misinformation can significantly impact health outcomes, for example by delaying healthcare-seeking. Understanding how rumours and misinformation spread can inform strategies such as proactive 'pre-bunking' to counter its effect.	Very high	Social listening and infodemiology. Randomised controlled trials of interventions, for example on the effectiveness of different 'truth sandwich' messaging formats.

Zoonosis prevention: How can communities be engaged in environmental and zoonotic management without compromising livelihoods?	Zoonotic spillover is linked to land use and the bushmeat trade. Research is needed on how to engage communities in One Health practices without destroying livelihoods. Partnerships often dissolve post-emergency. Efforts are needed to sustain these 'information loops' as part of routine health system strengthening.	Very high	Rich ethnographic assessments, One Health behavioural assessments; socio-ecological modelling; community-led zoonotic risk mapping. Feedback mechanisms and community partnerships. Medium: Implementation science studies on the transition from 'emergency RCCE' to 'routine health promotion'; stakeholder network analysis.
Wildlife trade: What cultural and economic factors drive wildlife trade in areas in which MPXV is endemic in animal populations?	Capture of wild animals and export of live animals or bushmeat creates opportunities for the dissemination of MPXV to new areas and zoonotic spillover. An understanding of the main cultural and economic factors influencing commercial wildlife trade is critical to the design of One Health interventions to reduce the risk of dissemination and spillover.	Very high	Rich ethnographic assessments, One Health behavioural assessments; socio-ecological modelling.

Subtheme 2: Stigma, discrimination and inclusive language

How do stigma, discrimination and communication practices shape access to care, participation in research, and uptake of medical countermeasures during mpox outbreaks, and what strategies can mitigate these barriers across contexts?

Knowledge gaps	Rationale	Importance	Approach
Measuring and monitoring stigma			

Metrics: How can context-sensitive tools be developed and validated to measure mpox-related stigma across different epidemiological and sociocultural contexts?	Without valid and reliable measurement tools, it is difficult to quantify stigma, to track changes across time, or to evaluate interventions designed to improve uptake of diagnostics, vaccines and treatment by addressing stigma-related barriers.	High	Co-creation and validation of stigma scales. Cross-country survey studies. Mixed-methods participatory research to adapt and test measurement tools across contexts.
Shifts in attitudes: How do the dynamics of stigmatisation evolve between 'routine' periods and acute health emergencies?	Insufficient comparative analysis prevents the design of flexible response strategies. Understanding these shifts allows for 'pre-emptive' anti-stigma campaigns that can be activated immediately during a surge.	High	Longitudinal comparative studies between routine and emergency periods to identify shifts in stigmatisation dynamics and social hostility.
Leveraging surveillance: How can mpox surveillance and response systems be leveraged to track stigma and discrimination?	Integrating standardised stigma indicators into surveillance systems could help identify emerging social barriers to MCM uptake and shape information response strategies.	High	Integration of behavioural monitoring into surveillance systems. Development of harmonised stigma indicators for use in surveillance activities. Implementation research on feasibility and data use.
Understanding and addressing the impacts of stigma			
Long-term consequences: What are the long-term impacts of mpox-related stigma?	Stigma may have multiple impacts on those affected, some of them mediated through impacts on access to mpox care. Addressing the 'long tail' of stigma is essential for the sustainability of health systems. Evidence would enable the development of engagement strategies that maintain community trust after an acute crisis ends.	High	Longitudinal cohort studies monitoring community sentiment and mental health outcomes, ethnographic studies on post-outbreak resilience, and embedding community-led civil society engagement within the public health surveillance structures.

Systemic factors: How do legal and structural environments influence mpox reporting, testing and care-seeking behaviours?	Structural barriers, including the criminalisation of sex work and same-sex relationships, may discourage individuals from accessing health services or reporting their symptoms. This can undermine outbreak detection and control.	Very high	Comparative policy analysis. Mixed-methods implementation research. Cross-country studies that examine legal environments and health service utilisation. Developing an index that measures community-led civil society engagement within public health decision-making for cross-country and cross-time comparisons.
Impacts on caregivers: How are caregivers (including health workers) affected by stigmatisation of mpox?	In stigmatising environments, healthcare workers and informal carers may experience socio-behavioural burdens, secondary discrimination and mental health impacts. Understanding these impacts will help to ensure that carers receive the appropriate support and are able to deliver high-quality care to those affected by mpox.	High	Rapid ethnographic surveys Mixed-methods social and behavioural research Qualitative interviews Community perceptions- focus group discussions
Clinical trials: To what extent does discrimination act as a barrier to clinical trial participation?	Stigma and discrimination could lead to unwillingness to participate in research. This has implications for both equity (access to novel interventions in certain communities) and scientific validity (potentially biased samples). Reducing discrimination provides the 'social safety' required to increase enrollment in trials and improves adherence to treatment regimens.	High	Mixed-methods studies on trial recruitment barriers.

Addressing stigma: What is the role of community mobilisation and decriminalisation in improving response to mpox?	Stigma and discrimination shape access to care and uptake of MCMs. There is limited awareness of whether approaches such as risk communication, information sharing and community engagement reduce stigma.	High	Formative studies to develop a theory of change (ToC) for stigma-reduction interventions, reduction of stigma and increased uptake of MCMs. Use of implementation studies and process evaluation to measure the effect of the intervention component and ToC.
Inclusive language: How can inclusive language frameworks tailored to diverse cultural and linguistic contexts be developed and validated?	Lack of linguistically sensitive communication can lead to public misunderstanding of MCMs. Validating inclusive frameworks reduces friction in official messaging, ensuring regulatory information and safety data are accessible to all.	Very high	Discourse and linguistic analyses to assess the impact of terminology in official and media communications; community-based validation workshop and corpus linguistic approaches.

Subtheme 3: Care-seeking and service pathways

How do social, structural and economic factors influence the journey from symptom onset to recovery, and how can pathways be optimised to ensure equitable access to care?

Knowledge gaps	Rationale	Importance	Approach
Care pathways			
Care-seeking behaviour: What are the specific help-seeking trajectories of mpox patients, from initial symptom onset to specialised clinical care?	A lack of systematic data on care pathways prevents health systems from adapting to local realities related to care seeking and impacts the distribution of MCMs. Mapping these journeys allows for the strategic placement of diagnostics and treatments where patients first seek help.	Very high	Rapid ethnographic assessments, qualitative interviews, patient accounts documenting experiences with traditional healers and formal providers, and focus groups.
Routine vs outbreak: How do care pathways differ between routine and emergency (outbreak) situations?	Understanding this shift is essential for building resilient MCM delivery systems that do not collapse under pressure. In addition, identifying how structural barriers develop or intensify during crises can be used to ensure the inclusion of vulnerable populations.	Very high	Quantitative population surveys on consultation times and satisfaction; comparative statistical analyses of emergency vs normal pathways; use of rapid ethnographic assessment methods to conduct time-motion studies.
Special populations			
PLHIV: How do the unique social circumstances and clinical needs of people living with HIV (PLHIV) influence their mpox care-seeking behaviour?	Data are rarely disaggregated for PLHIV, despite their higher risk for severe mpox outcomes. PLHIV may also have regular contact with health systems, creating opportunities for HIV service integration	Very high	Qualitative interviews with PLHIV and service providers; journey mapping specifically for treatment-non-adherent cohorts.

	to be a primary vehicle for mpox MCM delivery.		
Gender: How do gendered burdens and intersectional vulnerabilities (age, occupation, status, intersectional identities) dictate access to care?	Women often manage care for others while lacking financial control over their own treatment. Intersectional research ensures that response strategies account for the double burden of care-seeking and care-giving.	High	Gender-stratified secondary data analysis and intersectional qualitative studies (examining age, gender, occupation, and economic status) and community-based participatory research. Power mapping and ethnographic case studies.
Pregnant women: How do the unique clinical and social experiences of pregnant women influence their care-seeking behaviours and access to mpox MCMs?	Recent studies have highlighted several significant concerns associated with this infection during pregnancy.	Medium	Qualitative interviews and surveys with pregnant women and recent mothers, recovered patients and healthcare workers. Mapping of patient journeys.
Children and adolescents: How do social attitudes affect care-seeking behaviours of caregivers and adolescents?	An understanding of these factors will inform the design of care pathways suitable for these age groups.	Medium	Qualitative interviews and surveys with caregivers, adolescents and healthcare workers. Mapping of patient journeys.
Mobile and displaced populations			
Mobile populations: What are the care-seeking behaviours of migrant workers and other mobile populations?	In at-risk countries, many community members temporarily relocate to access work opportunities or regularly cross borders. A deeper understanding of attitudes, behaviours and care-seeking in these groups could inform risk-communication activities and health service provision.	High	Rapid ethnographic assessments, qualitative interviews, and focus groups.

Displaced populations: What are the unique care-seeking dynamics for displaced populations in conflict-affected zones?	Displaced populations (e.g. in eastern DRC) face broken referral chains and lack of trust in temporary health posts, often relying on unofficial channels.	Very high	Rapid ethnographic assessments in camps for internally displaced people (IDPs) and refugees, informal settlements and borderlands. Conflict-sensitive health system mapping and development of local conflict-sensitive frameworks to inform health responses.

Barriers			
Understanding health seeking behaviour: Which social and cultural determinants (stigma, gender, socioeconomic status) most significantly delay the search for care?	Improving health system resilience requires robust data on the 'why' behind delayed care. Addressing these determinants allows for the planning of more effective, culturally competent crisis responses.	Very high	Participatory studies, surveys and longitudinal studies to describe the social and cultural determinants of health seeking and document community-identified obstacles.
Structural barriers: How do structural barriers impact patient access to care?	Quantifying the impact of barriers such as travel distance, direct/indirect costs, and the availability of MCMs could help to improve access to care.	Very high	Participatory studies: Action research and visual methods (photovoice and journey mapping) to document community-identified obstacles. Use implementation research methods to evaluate approaches to decentralise MCM use, e.g. community caregiver cadres supported by electronic clinical monitoring tools, mobile services, and other community structures. Interventional pilot projects (mobile clinics, teleconsultations); impact assessments on the equity of these innovative care models.
Care quality: How does the quality of care provided affect uptake of services and adherence to public health measures?	The quality of services provided and users' experience of care promote adherence to clinical interventions and public health measures, and increase the real-world utility of R&D investments.	High	Longitudinal studies: Monitoring patients over time to analyse continuity of care, their experience of care and clinical outcomes before, during and after crises. Community-led monitoring and service user interviews.
Health system organisation			
Integration: What are the optimal strategies for integrating mpox care into existing health systems and coordinating these efforts with community-based interventions?	Mpox care often exists in silos. Researching integration pathways into primary healthcare ensures that responses are sustainable, less stigmatising, and leverage existing trust within community-led health structures to improve service delivery.	Very high	Health system studies: Policy analysis and service organisation mapping; international comparative studies to identify and transfer best practices across different epidemiological contexts. Costing analyses and mathematical modelling of cost-effectiveness.

Traditional healers: How can traditional healers and herbalists be formally integrated into the mpox referral and surveillance networks?	In many endemic regions, traditional healers are patients' first point of contact. Excluding them from the 'official' roadmap can lead to missed cases and the spread of misinformation.	High	Participatory action research to co-design referral protocols between traditional healers and formal health clinics.
Other health care workers: What role can groups such as pharmacists play in mpox care?	Community pharmacists are a common first port of call in many settings and can play a key role in surveillance, treatment of mild cases and referral.	High	Mapping of current involvement in mpox care. Participatory action research to identify optimal roles in care pathways.
Adherence to public health measures			
Isolation: How can financial barriers affecting adherence to isolation guidance be overcome?	In resource-limited settings, a 21-day isolation period often results in total loss of income. Without economic 'cushions', adherence to isolation is practically impossible for informal workers.	High	Socio-economic impact assessments and randomised controlled trials of 'cash-plus' interventions (cash transfers plus medical care).

Subtheme 4: Vaccination confidence, behaviour and delivery			
How do behavioural, social and structural factors shape the acceptability of and demand for mpox vaccines, and how can vaccination strategies be optimised to improve uptake of medical countermeasures across diverse contexts?			
Knowledge gaps	**Rationale**	**Importance**	**Approach**
Risk perception			

Demand: How do contextual factors (e.g. risk perception, institutional trust, stigma) influence the acceptability of and demand for mpox vaccination?	Optimising the implementation of MCMs requires a granular understanding of vaccination behaviours to adapt distribution strategies to local social realities.	High	Rapid ethnographic assessments, qualitative interviews, surveys, focus groups to explore fears and motivations, and ethnographic studies on local social dynamics.
Risk perception: How do perceptions of mpox risk and perceived benefits or harms of vaccination influence vaccine acceptance and uptake?	Risk perception significantly influences vaccine decision-making and may affect willingness to seek vaccination during outbreaks.	Very high	Behavioural surveys; discrete choice experiments; in-depth interviews; focus group discussions across different populations.
Pregnant women: What are the specific perceptions, safety concerns and access challenges regarding mpox vaccination among pregnant women?	While clinical trials for pregnant women are advancing, understanding of specific behavioural drivers in this group is limited. Closing this gap is critical for maternal and neonatal protection.	Very high	Rapid ethnographic assessments with rapid qualitative assessments (in-depth interviews and focus group discussions) with pregnant women and antenatal providers.
Routine vs outbreak: How do vaccination behaviours and trust dynamics shift between 'routine' health periods and acute emergency contexts?	Understanding this shift is vital to strengthen community buy-in and reduce resistance during mass campaigns, ultimately ensuring higher population coverage during an outbreak.	Very high	Rapid ethnographic assessments, quantitative population surveys, and comparative statistical analyses of coverage and barriers.
Other demand-side barriers			
Financial barriers: How do financial and practical barriers, such as travel costs, lost income and service fees, influence mpox vaccination uptake?	Economic constraints may limit access to vaccination and reduce uptake of medical countermeasures in low-resource settings.	High	Economic and behavioural studies assessing cost barriers.
Supply-side barriers			

Access: Which structural and logistical barriers (dose availability and centre accessibility) most significantly impede equitable vaccine access?	Identifying these bottlenecks allows for the inclusion of vulnerable and hard-to-reach populations through targeted delivery models.	High	Interventional pilot projects (mobile clinics, school-based campaigns, peer-led community mobilisation, and demand creation); systems analysis; impact assessments on campaign equity.
Optimising delivery			
Community delivery: How can administration practices be optimised (e.g. through community health workers or task shifting) to increase resilience?	Robust data on delivery methods (choice of sites and role of community health workers) will facilitate effective planning and ensure mpox vaccination is integrated sustainably into routine programmes.	Very high	Rapid ethnographic assessments, behavioural surveys, discrete choice experiments, in-depth interviews across diverse populations and interventional studies
Community preferences: What are community preferences regarding mpox vaccine delivery characteristics, including dose schedule, administration route, and vaccination settings?	Understanding product and service-provision preferences can inform vaccine rollout strategies and also improve acceptability and uptake of vaccination programmes.	Very high	Discrete choice experiments. Qualitative studies that evaluate preferences for vaccine attributes and delivery models. Interventional research (e.g. cluster randomised or stepped-wedge trials with realist process evaluation), testing the impact on vaccine demand creation of different combinations of approaches to community mobilisation and decentralised vaccine delivery.

Subtheme 5: Implementation research for systems integration

How can health systems and surveillance infrastructures be optimised and integrated to ensure the equitable, timely and scalable delivery of mpox medical countermeasures across diverse and resource-constrained environments?

Knowledge gaps	Rationale	Importance	Approach
Bottlenecks: What implementation bottlenecks affect the delivery of mpox medical countermeasures across diverse epidemic contexts?	Health system capacity, infrastructure and social conditions differ across contexts (including urban and rural settings and conflict-affected or displaced populations). Identifying barriers is important for ensuring that MCMs can be delivered effectively and equitably during outbreaks.	Very high	Implementation research (e.g. cluster randomised or stepped-wedge trials with realist process evaluation) that compares delivery models across contexts. Operational research evaluating barriers to testing, vaccination and treatment across settings.
Surveillance integration: How can mpox surveillance systems be effectively integrated, testing decentralised, and sample transport logistics and data systems strengthened to support timely outbreak detection and support response?	Improving surveillance integration, decentralised testing and efficient data systems can support earlier case identification and more effective deployment of behavioural and biomedical countermeasures. Operational and implementation research could generate evidence to enhance national surveillance systems.	Very high	Implementation research (e.g. cluster randomised or stepped-wedge trials with realist process evaluation) and operational studies assessing integrated surveillance models, decentralised testing strategies, and sample transport systems and outbreak response.

Subtheme 6: Engagement with R&D

How can social, behavioural and participatory research/co-production be integrated throughout the R&D lifecycle to build community trust, ensure ethical trial conduct, and maximise the social acceptability of mpox interventions?

Knowledge gaps	Rationale	Importance	Approach
Community perceptions: How do communities perceive and respond to the roll-out of medical countermeasures, including experimental or conditionally approved interventions, during acute mpox outbreaks?	Public understanding of conditional approvals, safety monitoring and improved guidance may influence trust, acceptance and adherence to vaccination and treatment strategies during emergency responses.	High	Rapid ethnographic surveys; mixed-methods social and behavioural research; qualitative interviews; focus group discussions. Communication strategy assessments during and after emergency roll-out of MCMs.
Strengthening trust: How can public understanding of and trust in science be strengthened to support trial preparedness, design and participation?	Public trust and understanding of research processes are essential for timely and ethical trial implementation during public health emergencies. Strengthening communication around research ethics, participant rights and the purpose of clinical trials can improve community engagement, facilitate recruitment and support ethical conduct of research during outbreak responses.	High	Qualitative and participatory research to assess community perceptions and understanding of clinical research and trial participation. Community engagement and communication studies evaluating strategies for improving research literacy and trust. Operational research examining best practices for information exchange and ethical communication during trial preparedness and implementation.
Achieving GPP: What are the most effective approaches for implementing Good Participatory Practices (GPP) during clinical trials conducted in emergency outbreak settings?	Effective community engagement and participatory practices are essential for ethical and acceptable trial implementation during public health emergencies. Applying GPP can help strengthen trust, ensure meaningful involvement of affected communities, and improve transparency and accountability in research conducted during outbreaks.	Very high	Implementation and operational research evaluating different GPP models during outbreak-related trials. Qualitative and participatory studies with community stakeholders, trial participants and implementers to identify best practices and challenges in emergency research contexts. Comparative case studies of participatory approaches used in different outbreak settings.

ENABLERS:

Enablers	Rationale	Importance	Approach
Capacity, community tools/resources and other enablers that would accelerate closing of knowledge gaps or overcoming of key barriers	*How these enablers would accelerate development of medical countermeasures*	*Very high, high, medium or low*	*Strategy for developing enablers*
Integration of social, behavioural and implementation research across the mpox R&D continuum	Incorporating social and behavioural science perspectives across the R&D continuum (including upstream R&D, product development and target product profile (TPP) specification, trial preparedness and design, trial implementation in emergency contexts, dissemination of trial findings, and product roll-out) can help ensure that medical countermeasures are acceptable, feasible and responsive to community needs. Engaging key stakeholders, including affected communities, can strengthen trial design and implementation, improve trust in research processes, and support the equitable dissemination and uptake of medical countermeasures.	Very high	Stakeholder consultations and participatory research with community representatives, policymakers, researchers and implementers. Qualitative studies and workshops to identify research priorities across the R&D continuum. Participatory and community-engaged research approaches to inform trial design, implementation and dissemination strategies. Embedding community-led civil society engagement within the continuum of mpox research. Including social and behavioural science expertise on technical working groups (e.g. for TPP development).
Collaborations between social, behavioural and biomedical scientists and public health agencies/operations centres developed prior to health emergencies	Interdisciplinary approaches to outbreak response are essential. Collaborations help to bridge the gap between academic theory and operational reality, help to build trusting relationships, and ensure that experts are already vetted and familiar with public health workflows before a crisis hits.	High	Establish memoranda of understanding between institutions to facilitate collaborations and rapid engagement in health emergencies. Develop models of transdisciplinarity that harness insights across social sciences, humanities, public health, clinical medicine and basic science

Integration of social and behavioural evidence into all pillars of outbreak response before and during emergencies	Ensures that social and behavioural evidence is integrated and institutionalised into operations rather than treated as an afterthought, allowing for rapid, culturally sensitive MCM deployment that is not just a medical exercise but a socially grounded one. Pre-established mechanisms prevent the 'panic-and-forget' cycle and allow for trusted communication.	Very high	Integration of social, behavioural, humanities (e.g. linguistics and historians) expertise into coordination structures, including Incident Management Systems (IMS); cross-pillar training on social and behavioural evidence to drive end user demand. Policy advocacy to include social science as a core pillar in national outbreak response plans; development of standing social science sub-groups within MoH structures.
Strengthened South–South and South–North networking	Social and behavioural research studies in sub-Saharan Africa are typically small scale and isolated, due to a fragmented and often isolated research community. Strengthened South–South networking will support greater sharing of information and expertise, promote collaboration and larger-scale studies, and help to build methodological expertise. Greater South–North networking will deliver two-way benefits to social and behavioural researchers in both high-income and low-income settings working with communities affected by mpox.	Very high	Establish a dedicated South-South transdisciplinary network (coordinated by a body such as the Africa CDC) to promote knowledge and skills exchange and to institutionalise peer-to-peer methodological training. This framework will support regional researchers in transitioning from ad-hoc, reactive qualitative assessments into highly rigorous, theoretically grounded longitudinal cohort studies.
Standardised 'trust metric scales' and real-time digital feedback dashboards	Allows responders to pivot strategies in real-time if misinformation or distrust spikes. Data-driven trust monitoring ensures that MCM uptake is not hindered by undetected rumours.	Medium	Multi-disciplinary collaboration between data scientists, anthropologists and psychologists to co-design and validate indicators.

Pre-validated inclusive language frameworks and child-friendly messaging toolkits	Accelerates the production of communication materials during an outbreak. Having ready-to-use, non-stigmatising templates reduces friction and prevents the traumatisation of paediatric cohorts.	Very high	Community-based validation workshops to co-create messaging with marginalised groups, caregivers and paediatricians; linguistic audits of existing materials.
Social science research blueprints and ethics 'fast-track' protocols	Reduces the time between outbreak onset and research implementation. Pre-prepared protocols for rapid evidence production during acute events are critical for evidence-informed public health responses. Clinical trial protocols with embedded GPP ensure that ethical, community-led research can start immediately.	Very high	Pre-drafting generic 'master protocols' for social and behavioural operational studies (using quantitative, qualitative or mixed methods) and clinical trial protocols with integrated sections and resource allocation for GPP; establishment of emergency ethics review boards with social and behavioural science and community engagement expertise. Adapt existing materials (e.g. https://www.protocols.io/view/an-umbrella-protocol-for-qualitative-research-in-i-36wgqpee3vk5/v1).
'Stigma-shielding' infrastructure for clinical trial platforms	Stigma and criminalisation are severe barriers to trial enrollment and epidemiological data collection. Pre-approved, legal and operational safe-harbour protocols therefore need to be incorporated within clinical trial networks. This includes strict cryptographic data de-identification, secure off-site community testing facilities, and partnerships with trusted, peer-led civil society networks to provide absolute legal and social protections for participants from marginalised populations.	Very high	Stigma-shielding measures incorporated within clinical surveillance systems, clinical trial network operations, and clinical trial protocol development.

Decentralised testing and integrated surveillance data systems	Moves diagnostics closer to the community, reducing travel barriers and costs. Integrating behavioural indicators into these systems provides a holistic view of the outbreak.	Very high	Implementation research on mobile lab units and point-of-care testing; software development to include socio-behavioural fields in surveillance databases.

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