McMaster University | Health Forum

Rapid Evidence Profile

Identifying first-case response plans for clade I mpox

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[MHF product code: REP 91]

Context

- The World Health Organization (WHO) declared a Public Health Emergency of International Concern on 14 August 2024 in response to a significant increase in reported mpox cases and the rapid spread of a novel subclade, monkeypox virus (MPXV) clade Ib, in the Democratic Republic of Congo (DRC).(1)
- Since then, clade I mpox cases have been identified in several countries outside of Africa, including Sweden, Germany, the United States, the United Kingdom, and Canada, each with different public-health systems for managing communicable diseases.(2)
- This rapid evidence profile identifies the available evidence about approaches to first-case response plans within Canada and internationally for MPXV clade I and how they are capturing adaptation of responses for different first-case scenarios.
- Note that those interested in a broader overview of evidence about mpox should also see our living evidence profile with the best-available evidence related to the mpox outbreak.

Box 1: Evidence and other types of information

+ Global evidence drawn upon

Single studies selected based on relevance, quality, and recency of search

- No forms of domestic evidence used

+ Other types of information used

Jurisdictional scan (seven countries: EU, FR, DE, IT, JP, UK, US) and Canadian provinces and territories

*** Additional notable features**

Prepared in three business days using an 'all hands on deck' approach

Questions

What is known from the best-available evidence and experiences from Canadian and international jurisdictions about first-case response plans for clade I mpox?

High-level summary of key findings

- We identified six relevant single studies, including one pre-print study, that explored a few countries' responses to first cases of clade I mpox.
- Across these studies, polymerase chain reaction testing and whole genome sequencing were identified as laboratory diagnostics used to confirm first cases of clade I mpox when they presented at public-health facilities.
- The evidence indicates that contact tracing and case management began immediately in Germany and Sweden once first cases were confirmed, and quick actions by health authorities, as well as compliance of cases and their contacts, led to rapid containment of mpox in these countries.
- In contrast, evidence showed that settings of highly dense populations in which first cases were found, coupled with political instability in North Kivu province in the DRC, created conditions for rapid transmission of mpox.
- Additional research is needed to assess responses to first cases of clade I mpox in other countries outside of Africa.

- We conducted a jurisdictional scan of first-case response plans and guidance documents for clade I mpox from all Canadian provinces and territories, G7 countries (European Union, France, Germany, Italy, Japan, United Kingdom, and United States) and nine multinational organizations (Africa Centres for Disease Control and Prevention (Africa CDC), European Center for Disease Prevention and Control (ECDC), Pan American Health Organization (PAHO), World Health Organization (WHO), WHO – Africa, WHO – South-East Asia, WHO – Europe, WHO – Eastern Mediterranean, and WHO – Western Pacific).
- Among Canadian provinces and territories and G7 countries, there was limited information solely focused on clade I mpox as most response plans and guidance documents were generalized to all clades.
- Countries generally had response plans and guidelines in place that proactively guided how they responded to identification, prevention, and control of any clade of mpox, or they updated already existing plans to include information on clade I mpox.
- Some multinational organizations did publish response plans and guidance documents that were specific to clade I mpox and referred to guidance documents of Canadian and other jurisdictions as resources to support countries within their regions.

Framework to organize what we looked for

- Level of first-case response plan for clade I mpox
  - Provincial/territorial
  - National
  - International or multinational
- Components of a first-case response plan
  - Identifying and defining type of case (e.g., suspected, probable, confirmed case based on available evidence)
  - Using laboratory diagnostics (e.g., PCR testing, antigen-based rapid diagnostics tests, serology) and genomic sequencing to confirm case
  - Developing and/or strengthening monitoring and reporting approaches (e.g., use of real-time notification dashboards, ability to report findings across jurisdictions)
  - Implementing non-pharmaceutical measures to prevent and control transmission
    - case investigation and management
    - contact tracing and monitoring
    - exposure risk assessments and stratification tools (e.g., classification frameworks of exposure risk level, likelihood and impact estimates of importation)
    - management of mpox contacts (e.g., diagnostic test, regular practice of hand hygiene and respiratory etiquette, minimum physical contact)
  - Implementing pharmaceutical measures as part of public-health strategies
  - Other components not described above
- Broader components of an mpox preparedness and response plan
  - Governance arrangements (e.g., coordination, collaboration, and data sharing across related stakeholders such as government, public-health agencies, laboratories, surveillance systems across jurisdictions)
  - Financial arrangements (e.g., costs related to case management)
  - Delivery arrangements (e.g., risk communication and education, pharmaceutical measures)
- High-risk populations
  - Individuals travelling to and from countries in Africa with clade I mpox outbreaks (e.g., immigrants, visitors, African Canadians)
  - High-contact sexual networks (e.g., gbMSM (gay, bisexual, and other men who have sex with men), heterosexual individuals with high number of sexual partners, sex workers)
  - Refugees
  - Healthcare workers deployed to affected countries with clade I mpox outbreaks
- Outcomes related to containment of cases (e.g., spread of cases, prevention of secondary transmission)

What we found

We identified six relevant single studies, including one pre-print study, but no evidence syntheses relevant to the research question. Three of the studies described responses to first cases of clade I mpox in 2024, while the remaining three studies described responses to first cases of clade II mpox during the 2022 mpox outbreak. In the summary of key findings below, we highlight the similarities and differences in responses to first cases of mpox during the 2022 and 2024 outbreaks based on the evidence.

We also identified first-case response plans and guidance documents for clade I mpox from all Canadian provinces and territories, G7 countries (European Union, France, Germany, Italy, Japan, United Kingdom, and United States) and from nine multinational organizations (Africa CDC, European CDC, PAHO, WHO, WHO – Africa, WHO – South-East Asia, WHO – Europe, WHO – Eastern Mediterranean, and WHO – Western Pacific). We summarize the key findings from our jurisdictional scan based on categories of the organizing framework.

Coverage by and gaps in existing evidence syntheses and domestic evidence

The lack of existing evidence syntheses identified on first-case clade I mpox response plans indicates a gap in coverage of the evidence. Based on the evidence from the relevant single studies we did identify, we found some similarities in the way countries identified and diagnosed cases using laboratory diagnostics and in some of the measures used as part of public-health strategies. However, there was a lack of evidence on responses to first cases of clade I mpox in several countries outside of Africa, including Canada, the U.S. and the U.K. which are covered in more detail in the results below. There was limited evidence on the coordination of responses, including case management strategies and surveillance mechanisms, within countries as well as by multinational organizations. Future research in these areas should be explored to enhance the responses of all countries to first cases of mpox clade I and any future clades.

Box 2: Approach and supporting materials

At the beginning of each rapid evidence profile and throughout its development, we engage a subject matter expert and one or more citizen partners, who help us to scope the question and ensure relevant context is taken into account in the summary of the evidence.

We identified evidence addressing the question by searching PubMed, Health Systems Evidence and Social Systems Evidence for full evidence syntheses (or synthesis-derived products such as overviews of evidence syntheses), protocols for evidence syntheses, and single studies. All searches were conducted on 12 February 2025. The search strategies used are detailed in Appendix 1. We also conducted a jurisdictional scan of first-case response plans for clade I mpox from all Canadian provinces and territories, G7 countries (European Union, France, Germany, Italy, Japan, United Kingdom, and United States) and nine multinational organizations (Africa CDC, ECDC, PAHO, WHO, WHO – Africa, WHO – South-East Asia, WHO – Europe, WHO – Eastern Mediterranean, and WHO – Western Pacific). Where information is not available in English, French, Chinese, Portuguese, or Spanish, we attempted to use site-specific translation functions or Google translate.

In contrast to synthesis methods that provide an in-depth understanding of the evidence, this profile focuses on providing an overview and key insights from relevant documents.

We typically appraise the methodological quality of relevant evidence syntheses using the first version of the AMSTAR tool. However, there were no evidence syntheses identified for this profile.

A separate appendix document includes:

1) methodological details (Appendix 1)
2) details about each identified single study (Appendix 2)
3) details from the jurisdictional scan of Canadian provinces and territories (Appendix 3)
4) details from the jurisdictional scan of international countries and multinational organizations (Appendix 4)
5) documents that were excluded in the final stages of review (Appendix 5).

This rapid evidence profile was prepared in the equivalent of three days of a 'full-court press' by all involved staff.

Key findings from included evidence documents

We identified six relevant single studies, including one pre-print study, that explored responses to first cases of mpox. Three of these studies described responses in Germany, Sweden, and the North Kivu province of DRC to first cases of clade I mpox in 2024. The remaining studies described responses in four European countries and the United States to first cases of clade II mpox during the 2022 mpox outbreak. In the summary of key findings below, we highlight the similarities and differences in responses to first cases of mpox during the 2022 and 2024 outbreaks based on the evidence. We describe the findings below using the categories of the organizing framework.

Components of a first-case response plan

Identifying and defining the type of case, including using laboratory diagnostics

Across the three studies that explored first cases of clade I mpox, genome sequencing was used to confirm suspected cases. According to the 2024 study investigating Germany's response to the first imported clade I mpox case in an individual returning from Rwanda in October 2024, mpox diagnosis was first confirmed by PCR testing at a local health unit and molecular typing was used subsequently to confirm clade Ib mpox infection in the traveller.(3) Sweden's response to its first imported clade I mpox case was similar to Germany's, according to another 2024 study, where real-time PCR testing followed by whole genome sequencing was used to confirm clade Ib mpox infection in a Swedish traveller returning from Central Africa who presented immediately at an outpatient clinic after experiencing symptoms for several days in Africa.(4) In the recent pre-print study based in the DRC that reported on the first introductions of clade Ib mpox cases in North Kivu province, investigators indicated that PCR testing and whole genome sequencing were used to confirm clade Ib mpox infection in swabs taken from the first cases.(5)

There were no definitions for types of mpox cases described in the studies based in Germany and Sweden, but the DRC study included the DRC Ministry of Health's definition of a suspected case, characterized by the presentation of lesions, symptoms such as fever and pustules, and past exposure to a suspected case or wild animal with lesions.(5)

One of the single studies that focused on responses to the 2022 outbreak of clade II mpox in nonendemic countries found that Italy and Spain defined cases according to the WHO's criteria (four categories: suspected, probable, confirmed, and discarded) while France and Portugal used their own case definitions (three categories: suspected/possible, probable, and confirmed).(6) Heterogeneity was found in the case definitions of these European countries. There were no specific details provided in the two U.S.-based studies on how the first mpox cases were defined and confirmed via laboratory testing.(7; 8) However, it was noted that identification of mpox was delayed for several days after the first mpox case presented in the U.S. in late April 2022 since potential for community spread of mpox in nonendemic countries was not yet understood. This led to the spread of mpox to multiple contacts across several health facilities in Massachusetts where the first case presented.

Implementing non-pharmaceutical measures to prevent and control transmission

In response to the first confirmed clade I mpox case returning to Germany from Rwanda, the federal state public-health institute was notified by the local department of health in Cologne. Molecular typing to confirm MPXV clade Ib was conducted, and a risk assessment was performed by the Robert Koch Institute (RKI), the national public-health institute. RKI also informed the Rwanda Ministry of Health, ECDC, and the WHO's Regional Offices for Europe and Africa.(3) Contact tracing began immediately after confirmation by the local health department using a contact definition of anyone who was exposed to the patient while the patient was symptomatic, regardless of personal protective equipment (PPE) use. A total of 34 contacts (all considered low risk) were identified across six local health departments and all were followed for 21 days after their most recent exposure to the case. Since most contacts were medical staff who used PPE when in contact with the mpox case, increased spread of the mpox infection was averted.

According to the study that investigated the response to the first clade Ib mpox case in Sweden, the patient self-isolated and used a face mask and covered lesions in public spaces following the appearance of the first lesion.(4) The patient also had a travel companion who developed symptoms of a mild sore throat after arrival in Sweden and was monitored for 21 days, testing negative for mpox during this period. No contact tracing occurred since the patient had no contact with anyone other than the travel companion. Public-health measures were implemented by the Public Health Agency of Sweden (PHAS) to advise the public on pre- and post-travel behaviour, update mpox practice guidelines for healthcare practitioners, and increase surveillance of open-source information, media, and scientific literature for updates on mpox.

Case investigations and epidemiological analysis of the first cases of clade Ib mpox in the North Kivu province of DRC indicated that non-sexual transmission of mpox occurred in close non-intimate contacts and children.(5) Mpox cases were also identified at a displaced persons site where there were poor sanitation conditions, very limited healthcare support, and highly dense populations. The DRC study highlighted the importance of greater community engagement to enhance recognition and reporting of cases and inform communities about the risks for mpox in children.

Following confirmation of the first clade II mpox case in the U.S. in Massachusetts in May 2022, a framework for exposure risk assessment and stratification was developed to classify degrees of exposure to the first case patient and provide guidance on appropriate preventative measures for contacts.(7) Exposure risk assessments, contact tracing and symptom monitoring were used to control the spread of mpox infection. All contacts were monitored for symptoms during the 21-day period following their last exposure. Within Massachusetts General Hospital specifically, a Research Electronic Data Capture (REDCap)-based system, which included automated exposure notifications, risk stratification, and daily symptom monitoring (i.e., via e-mail or SMS), was implemented to notify healthcare personnel of possible exposure, assess and stratify their risk, and monitor symptoms for 21 days.(8)

Implementing pharmaceutical measures as part of public-health strategies

In terms of pharmaceutical measures implemented in first-case responses to clade I mpox, post-exposure vaccination was offered to all contacts of the first case in Germany and vaccine protocols were updated in Sweden to recommend mpox vaccination prior to travel to areas with ongoing transmission of clade I mpox.(3; 4) Pharmaceutical measures were not addressed in the DRC-based study.(5)

Post-exposure prophylaxis was offered to high-risk contacts of the first mpox case in 2022 in the U.S.(7)

<u>Broader components of an mpox preparedness and response plan</u>

Across the three studies that described countries' responses to the first cases of clade I mpox, coordination and collaboration between government agencies and health-system interest holders varied, resulting in different outcomes. In Germany, a comprehensive response consisting of the local health unit in Cologne conducting PCR testing, confirming the first case's diagnosis and notifying the federal public-health institute, immediately led to a risk assessment being performed by RKI and notification of all relevant international stakeholders (e.g. Rwandan government, WHO) before contact tracing began.(3) Resources were made available to monitor all contacts and offer vaccination to quickly contain the spread of mpox. A potential mpox outbreak was averted in Sweden not only because health officials responded quickly to contain transmission when the first case presented at the outpatient clinic in Stockholm, but also because the first-case traveller and their travel companion self-isolated immediately after arriving in Sweden.(4) According to the study, PHAS also implemented several public-health measures to prevent any future spread of clade I mpox. Finally, the DRC study indicated that the highly dense settings in which the first cases were found, coupled with political instability in North Kivu province, created conditions for rapid transmission of mpox.(5)

These findings highlight the importance of responding quickly to identify, diagnose, and implement a coordinated response to contain transmission and alert other countries and regions of mpox transmission.

Key findings from jurisdictional scans of Canadian provinces and territories, other countries, and multinational organizations

We conducted a jurisdictional scan of first-case response plans and guidance documents for clade I mpox from all Canadian provinces and territories, G7 countries (European Union, France, Germany, Italy, Japan, United Kingdom, and United States) and nine multinational organizations (African CDC, European CDC, PAHO, WHO, WHO – Africa, WHO – South-East Asia, WHO – Europe, WHO – Eastern Mediterranean, and WHO – Western Pacific). Among Canadian provinces and territories and G7 countries, there was limited information solely focused on clade I mpox as most response plans and guidance documents were generalized to all clades. Countries generally had response plans and guidelines in place that proactively guided how they responded to identification, prevention, and control of any clade of mpox, or they updated already existing plans to include information on clade I mpox. Some multinational organizations published response plans and guidance documents that were specific to clade I mpox and referred to guidance documents of Canadian and other jurisdictions as resources to support countries within their regions.

We organized the findings of our jurisdictional scan by components of a first-case response plan, in alignment with the organizing framework. We also described some features of broader components of mpox preparedness and response plans as well as any outcomes related to the containment of mpox spread after response measures were implemented.

Components of a first-case response plan

Identifying and defining type of case

Across the mpox response plans of Canadian provinces and territories, similar definitions for confirmed, suspected, and probable cases were used to identify mpox cases. However, definitions were not specific to clade I mpox cases. According to mpox guidelines from Alberta, Manitoba, Ontario, Quebec, Nova Scotia, Newfoundland and Labrador, and Prince Edward Island, suspected cases are defined by the presence of a rash or ulcer, with symptoms not attributed to another diagnosis; probable cases are defined by unexplained acute rashes or lesions, with an epidemiological link to a confirmed mpox case or location of transmission; and confirmed cases are defined by confirmation of mpox through laboratory testing and/or genomic sequencing. The Government of Canada uses a general case definition for mpox cases and identifies a suspect case as presenting with an unexplained acute skin, genital, perianal, anorectal rash or lesions and at least one symptom (e.g. headache, fever, back pain, myalgia, fatigue, pharyngitis, proctitis (rectal inflammation)); a probable case as someone who meets the criteria of a suspect case and has an epidemiological link to a probable or confirmed mpox case or a location/event where transmission of mpox is suspected or known in the 21 days before symptom onset; and a confirmed case as having laboratory-confirmed mpox virus.

Several of the response plans and guidelines of other G7 countries included definitions of types of mpox cases, classifying them as suspected, probable, and confirmed cases based on specific qualifiers. These classifications align with guidance documents from the WHO, the U.S. Centers for Disease Control and Prevention (CDC) and ECDC. In these documents, definitions for clade I mpox cases are: 1) a suspect case, having probable or confirmed mpox alongside at least one of the clade I epidemiologic criteria; 2) a probable case, having probable or confirmed mpox, the clade I epidemiologic criteria, and clade I and clade II MPXV-negative by PCR testing without next-generation sequencing of a clinical specimen to confirm clade; and 3) a confirmed case, having the demonstrated presence of clade I MPXV DNA via PCR testing or next-generation sequencing of a clinical specimen.

Using laboratory diagnostics

Mpox response plans and guidance documents of most Canadian provinces (British Colombia, Alberta, Manitoba, Ontario, Quebec, Nova Scotia, Newfoundland and Labrador, and Prince Edward Island) indicated that clade I mpox cases are confirmed through real-time PCR testing and/or genomic sequencing. In alignment with WHO recommendations, PCR testing or genomic sequencing is also recommended to confirm clade I mpox cases in most G7

countries we reviewed (France, Italy, Germany, Japan, Canada, the U.K., and the U.S.). We did not identify any specific responses related to laboratory diagnostics for clade I mpox in these countries, outside of reporting any PCR-confirmed mpox cases to the national public-health authority.

In its mpox global strategic preparedness and response plan, the WHO recommends that Member States implement a standardized system to decentralize laboratory capacity and data exchange protocols and expand diagnostic testing to include the deployment of point-of-care diagnostics and sample referral networks. Following confirmation of the first known U.S. clade I mpox case in California, the U.S. CDC collaborated with public-health and government agencies to enhance laboratory diagnostics, surveillance measures, education of clinicians, and capacity to report case data. Africa CDC's mpox testing strategy provides testing strategies based on the different disease transmission settings (e.g., no/low cases, sporadic cases, cluster cases, widespread community transmission) for optimal outbreak response. According to the technical bulletin (September 2024) of the WHO – South-East Asia, planning for genomic sequencing for diagnosis, characterization, and monitoring of mpox virus is crucial and strongly encouraged. Similarly, ECDC emphasizes that nucleotide sequencing and sharing sequence information through public databases is an essential component to monitoring the mpox epidemiological situation in Europe and globally. PAHO continues to work with clinicians in Member States to disseminate information on the clinical features, management, and diagnostic challenges of suspected and confirmed mpox cases.

Developing and/or strengthening monitoring and reporting approaches through enhanced surveillance and research

We identified a few approaches taken by Canadian provinces and G7 countries to strengthen monitoring and reporting of clade I mpox cases. Wastewater monitoring of all mpox clades is being done in some Canadian provinces, in collaboration with the Government of Canada, which maintains a dashboard reporting on mpox virus detections in wastewater samples. The Government of Canada also conducts rapid risk assessments of mpox, and in its latest rapid risk assessment of clades Ia and Ib mpox (assessment completed 4 September 2024), details were provided on the likelihood and impact estimates of importation and transmission of clades Ia and Ib mpox cases, as well as proposed actions for public-health authorities with respect to risk communication, collaboration and coordination, and surveillance and reporting.

Following the 2022 mpox outbreak in Europe, the European Union invested in multiple mpox-related clinical research initiatives to strengthen monitoring and surveillance of mpox, including MPX-RESPONSE, VERDI, VEO, and projects led by Global Health EDCTP3 (an Africa-Europe clinical research partnership). Using evidence from an observational study and three randomised control trials, MPX-RESPONSE aims to build understanding of mpox and evaluate potential treatment options while VERDI aims to track and enhance understanding of mpox clinical features, risk factors, and treatment options for severe mpox in children and adults, including pregnant women. VEO has created an infectious disease observatory and is generating knowledge around clade I mpox epidemiology and evolution, and Global Health EDCTP3 is leading nine ongoing projects, run by research consortia in Africa and Europe, to address mpox surveillance, virology, epidemiology, and vaccine safety and immunogenicity in mothers and infants.

The RKI continues to monitor mpox cases in Germany closely and assess risk of exposure to the general population. Research is ongoing regarding the link between MPXV clades and disease severity. While there have been no reports of clade Ia or Ib mpox cases specifically in Italy, a surveillance system was established in Italy after its first case of clade II mpox was identified in May 2022 to monitor mpox cases in the country, and confirmed cases of any clade are reported to international organizations (WHO and ECDC) and published on the institutional portal. In Japan, the Ministry of Health, Labour and Welfare (MHLW) and related ministries developed response plans in accordance with the WHO's Public Health Emergency of International Concern declaration on mpox clade I. The Cabinet Office and MHLW jointly issued a notice to local governments and research institutes requesting rapid clade identification testing and directing them to maintain testing systems and submit samples from cases with overseas travel history. Physicians in Japan are also required to report suspected and confirmed cases to the local health authority.

In February 2024, in preparation for a potential clade I outbreak in the U.S., the federal government coordinated an incident response structure that consisted of outbreak simulation, wastewater surveillance, laboratory testing, vaccination, and review of treatment options for the rapid detection, containment, and management of emergent clade I mpox cases. The U.S. CDC also issued guidance for the clinical and public-health management of clade I mpox alongside clade I-specific and general mpox recommendations for clinicians to report suspected clade I mpox cases to the appropriate public-health laboratory within 24 hours and facilitate clade-specific testing, in addition to submitting case information in line with U.S. CDC reporting recommendations.

These approaches to monitoring and reporting on clade I mpox cases align with the guidance and recommendations of the Africa CDC, ECDC, PAHO, and WHO. These recommendations include integrating mpox surveillance into existing platforms (e.g., the Integrated Disease Surveillance and Response (IDSR) system used by Africa CDC), including mpox in the list of notifiable diseases, implementing event- and indicator-based surveillance systems, and implementing a standardized system to report quarterly to WHO on the implementation of temporary recommendations by Member States. The WHO and collaborating partners have also developed and used analytic tools for surveillance purposes, such as the Go.Data platform (an open-source outbreak tool for real-time analyses to inform field operations), the global repository of epidemiological parameters (GREP), PAHO's mpox cases dashboard, and analytics used by the WHO Hub for Pandemic and Epidemic Intelligence.

Implementing non-pharmaceutical measures to prevent and control transmission

Canadian provinces and territories as well as G7 countries and multinational organizations provided similar recommendations in their mpox response plans for implementing non-pharmaceutical measures to prevent and control transmission of all clades of mpox.

Case management and contact tracing

The most common non-pharmaceutical measures identified in response documents (Manitoba, Ontario, Prince Edward Island, Nova Scotia, and Nunavut) were contact tracing and isolation for probable and confirmed cases. Local public-health authorities in Canada are responsible for contact tracing of mpox cases, regardless of clade, based on evidence suggesting infection and transmission of up to four days before symptom onset. The Government of Canada advises that isolation measures for confirmed mpox cases include staying in separate spaces with the exception of a healthcare worker or professional with relevant infection, prevention and control measures, no travelling to other locations, no sharing of clothes and bedding, no blood donations, postponing any elective medical visits, using PPE, and disinfecting areas and surfaces. Additionally, post-recovery risk reduction should include the use of condoms for 12 weeks post-mpox infection. The Ontario Ministry of Health has advised that self-isolation may not be necessary for some mpox cases if lesions are covered and symptoms are mild, and isolation is not required for asymptomatic contacts who follow risk mitigation measures. Hygienic practices, including covering lesions and masks, hand washing, disinfecting common areas, avoiding shared materials (e.g., linens and utensils), and securely disposing of personal waste are recommended in most provincial guidance documents.

All countries that addressed case investigation and management in their response plans or guidelines (Germany, France, Italy, Canada, and U.S.) recommend that suspected and confirmed cases should isolate immediately until mpox symptoms resolve. This is echoed in ECDC's rapid risk assessment of the clade I mpox epidemic. France requires all probable or confirmed clade I mpox cases to be investigated (through questionnaire and contact tracing) by regional health agencies to identify contamination sources and stop transmission chains. Investigations should proceed without waiting for clade confirmation. RKI recommends isolation in a private room with separate bathroom (ideally), use of separate bedding and household items, and refraining from all sexual activities until symptoms subside and scabs heal or fall off. The U.K. Health Security Agency uses a contact classification system for contact tracing that is based on exposure risk, ranging from high (category 3: unprotected direct contact or high-risk environmental exposure) to low (category 1: protected physical or droplet exposure or no physical contact with minimal droplet risk). The U.S. CDC

advises that clinicians and health departments trace the contacts of people with suspected, probable, or confirmed clade I mpox, going back four days prior to the onset of illness.

WHO provides resources to countries for contact tracing and management of mpox cases (either clade). Africa CDC indicated in its response plan that it aims to develop tailored approaches for case management of patient populations such as children, youth, pregnant women, commercial sex workers, and other key groups. Other approaches for case management recommended by WHO regional offices (Africa, South-East Asia) include implementing clinical, psychosocial, and nutritional protocols, improving supply provision, building healthcare worker capacity, prioritizing supportive care, and offering home-based management for mild or uncomplicated cases under proper IPC conditions and facility-based management for high-risk or severe cases.

Classification frameworks of exposure risk level, likelihood, and impact estimates of importation

Limited information about exposure risk assessments and stratification tools was identified. In the technical annex of its latest rapid risk assessment of clades Ia and Ib mpox in Canada (assessment completed 4 September 2024), the Government of Canada provides key definitions and mathematical modelling to estimate the likelihood of importation and transmission of clades Ia and Ib mpox cases. The U.K. Health Security Agency published a situational assessment framework in its technical briefing on preparedness and response for mpox clade I that outlines the risk level and probability of importation, potential for spread in the U.K. once introduced, severity of disease, and possible countermeasures. The U.S. CDC also conducts clade I mpox risk assessments, identifying risk posed by the clade I mpox outbreak in the general U.S. population, children, and adults who have sex with members of the same sex or the opposite sex.

Additionally, the WHO provides resources such as the mpox triage and clinical assessment tool for suspected and confirmed cases, self-care and prevention fact sheets and a risk assessment tool for identifying and managing healthcare workers with a potential occupational exposure to mpox to assist countries in assessing risk of exposure to mpox. A framework has also been developed by the Government of Canada providing guidance to public-health authorities on the classification of contacts of mpox cases into high, intermediate, or low/uncertain risk categories based on the type and duration of exposure.

Managing mpox contacts

We identified some information on management of mpox contacts, especially as it relates to travel to and from countries where clade I mpox is circulating. The Government of Canada recommends that after public-health authorities identify and classify contacts as high, intermediate, or low risk, all contacts should implement basic public-health measures (e.g. hand hygiene, self-monitoring for symptoms, avoid donations of bodily fluids) and additional public-health measures (e.g. avoiding high-risk settings, wearing a medical mask, refraining from sexual contact) if contacts are identified as intermediate- or high-risk exposure contacts during the 21 days following mpox exposure. People from France travelling to countries where clade I mpox is circulating are advised to adhere to hygiene protocols, avoid close contact with infected individuals and animals, refrain from sharing personal items with potentially infected persons, monitor temperature and check for symptoms for 21 days upon return, and seek medical consultation if fever and blister-like rashes develop. France also emphasized the importance of raising awareness among health professionals of clade I mpox cases, travel links, varied clinical presentations, and differing transmission and affected groups. Public education about mpox was also highlighted as an approach of the Japanese government to proactively respond to clade I mpox outbreaks in other countries. Government agencies distributed educational materials and carried out community outreach via website postings and leaflets, and training sessions for medical institutions were provided to raise mpox awareness.

According to the UK Health Security Agency, high-risk contacts of mpox cases in the U.K. require active monitoring, self-isolation, and travel restrictions for 21 days, and they should be offered the MVA-BN vaccine within four days of contact

(within 14 days of contact for high-risk groups). The U.S. CDC has issued similar recommendations, advising that clade I mpox contacts with high exposure risk be monitored by the local health department for 21 days and those with intermediate exposure self-monitor for 21 days and restrict their activities in line with CDC guidance. Contacts with low risk of exposure are advised to self-monitor.

Across all multinational organizations, infection prevention and control measures were emphasized as key tools for reducing spread of mpox to contacts. The WHO and Africa CDC recommend strengthening these measures within households, schools, health facilities, and communities through comprehensive IPC guidelines, PPE supplies, and training. PAHO continues to monitor travel measures for mpox in 35 countries in the Americas, and confirmed in a recent situation report that there were no travel measures in these countries in response to the circulation of clade I mpox.

Implementing pharmaceutical measures as part of public-health strategies

Pharmaceutical measures implemented across most jurisdictions to mitigate the spread of clade I mpox involved vaccination with a third-generation smallpox vaccine (i.e., Imvamune in Canada, Imvanex in Europe, Jynneos in the U.S.). While the Government of Canada recommends that Imvamune vaccination be offered to all human contacts of mpox cases, response plans and guidelines of Canadian provinces and territories indicate that Imvamune vaccine is strongly recommended for individuals who are at high-risk of contracting mpox to prevent or reduce symptoms. High-risk contacts are defined in several response plans (Alberta, Quebec, Nova Scotia, and Newfoundland and Labrador) as men who have sex with multiple partners, individuals who have a previously confirmed sexually transmitted infection, individuals attending a sex-on-premise venue, sex workers, individuals who engage in sex tourism, or healthcare/research professionals who may be exposed. To facilitate delivery and administration of Imvamune vaccine to high-risk individuals, the government of B.C. coordinated with local health agencies, such as Vancouver Coastal Health, Immunize BC, Fraser Health, Interior Health, and Northern Health, to make the vaccine more accessible. In April 2023, the government of Nova Scotia expanded access to the Imvamune vaccine to physician offices and pharmacies enrolled in the Community Pharmacy Primary Care Clinic program, with pre-exposure vaccination being made available to certain high-risk populations. The New Brunswick government has advised in its 2024 mpox guidelines that antiviral medications with activity against orthopoxviruses be considered as treatment for mpox, and the Nunavik Regional Board of Health and Social Services has recommended antiviral treatment with tecovirimat as the first line of treatment for severe cases.

Pharmaceutical measures implemented by international jurisdictions also primarily consist of vaccination with Imvamune and treatment with tecovirimat (TPOXX). In the E.U., following the 2022 mpox outbreak, the European Medicines Agency (EMA) accelerated mpox vaccine and treatment development by advising product development, conducting clinical trials, fast-tracking approval processes, and creating a list of essential mpox medicines to mitigate shortages. Similar activities were undertaken in response to the 2024 outbreak of clade I mpox, during which Imvanex (Europe's version of the Imvamune vaccine) was used as mpox prevention for at-risk children under the age of 12 at the discretion of national health authorities. The EMA has also recommended extending Imvanex use to those aged 12 to 17 years.

Response plans described in the UK Health Security Agency's technical briefing indicate that vaccination is recommended for specific groups based on risk of transmission of mpox cases. For example, in a scenario where there is a controllable epidemic in high-contact sexual networks, vaccination would be expanded to sex workers and high-risk heterosexual people in addition to gay, bisexual, and other men who have sex with men (gbMSM), whereas in a scenario where there is community transmission in the general population through close contact, vaccination would be expanded to high-risk individuals and healthcare workers until global supply increases. France uses tecovirimat as the first-line treatment for mpox due to its oral availability and tolerance. Brincidofovir is used as the second-line option if available due to its oral administration and more favourable tolerance compared to cidofovir, which is only administered as the third-line treatment due to its injectable form, high toxicity, and potential risks. Vaccinia immunoglobulin (VIG) is reserved for pregnant women and children under 13 kg when antivirals are not an option.

In Japan, the LC16 vaccine, a smallpox vaccine developed in-country, has been approved for mpox prevention. Pre-exposure vaccination is recommended for healthcare workers, laboratory personnel, and high-risk groups (e.g., men who have sex with men with multiple sexual partners), and post-exposure vaccination is recommended for close contacts of mpox patients, ideally within four days of exposure. In terms of treatment, supportive therapy and pain control are recommended, and for severe cases and high-risk patients (e.g., immunocompromised individuals), antiviral drugs like tecovirimat are recommended.

The U.S. CDC , ECDC, PAHO, WHO – Africa, and WHO – South-East Asia recommend pre-exposure vaccination for targeted groups of individuals at high risk of exposure to an mpox case, and ECDC in particular, recommends post-exposure vaccination of mpox cases with a third-generation smallpox vaccine such as Imvanex.

Broader components of an mpox preparedness and response plan

In terms of coordination and data sharing in Canada, the Public Health Agency of Canada (PHAC) monitors mpox cases in Canada and supports provinces and territories in implementing a coordinated response to any cases (all clades) identified. Mpox has been nationally notifiable in Canada since August 2024, and it is reportable or notifiable in all provinces and territories. We found that coordination and data sharing of mpox cases and information in other countries had some similarities to Canada. In France, labs capable of clade determination must send clade I samples to the National Centre for Scientific Research for subclade analysis, and all confirmed cases are reported to the Santé publique France and published on their website. RKI continues to coordinate Germany's response to any clade I mpox cases in country by sharing information about cases with local agencies and international organizations, and in Japan, MHLW and related government ministries direct local government, research institutes, and quarantine stations on testing strategies to implement as the global mpox situation evolves. The U.S. federal government also took proactive measures in August 2024 to coordinate an incident response structure in preparation for a potential outbreak of clade I mpox in the U.S. Throughout the clade I mpox outbreak, the WHO and its regional offices have continued to use analytic tools to monitor clade I mpox cases globally and to coordinate the distribution of resources to support countries in managing cases.

We identified very limited information related to financial arrangements specifically geared towards clade I mpox response strategies. In the E.U., following the 2022 outbreak of mpox, 17 million euros of Horizon Europe funds was invested in developing the four mpox-related clinical research initiatives mentioned previously, MPX-RESPONSE, VERDI, VEO, and Global Health EDCTP3. Africa CDC provided an estimated budget for its mpox continental preparedness and response plan for Africa (excluding vaccine procurement) of US$599,153,498, of which 53% will support 14 of the member states affected by mpox. Additional information on how implementation of clade I mpox response measures as been or is being funded in countries may be forthcoming.

Next steps based on the identified evidence

While response plans have been implemented in countries outside of the DRC and surrounding countries in Africa to prevent and control the spread of mpox clade I, the evidence included in this rapid evidence profile highlighted several knowledge gaps that can be explored to improve countries' responses to first cases of clade I mpox or any future clades of the virus. Next steps to address these gaps may include:

- increasing the availability of high-quality evidence syntheses that assess how countries and multinational organizations have responded to first cases of mpox clade I in terms of identifying and confirming mpox infection and clade as well as case management and ongoing surveillance
- improving transparency in how the response measures detailed in mpox plans and guidelines will be funded by different levels of governments

- enhancing coordination and collaboration amongst all health authorities within national and global health system infrastructures to improve communication about first cases and subsequent cases of mpox within the health system and coordinate a cohesive response in order to mitigate spread
- providing evaluations of response plans to determine which responses were effective and strategies for improvement.

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