

Living Evidence Profile #6.1

(27 May 2022)

Question

What is the best-available evidence related to the monkeypox outbreak?

What we found

To inform current knowledge related to monkeypox, we identified evidence, as well as experiences from 11 countries (Australia, Belgium, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, United Kingdom (U.K.), and the United States (U.S.) (see Box 1 for a description of our approach), and from all Canadian provinces and territories. We organized our findings using the framework below.

Organizing framework

- Biology
- Epidemiology (including transmission)
- Prevention and control
- Clinical presentation
- Diagnosis
- Prognosis
- Treatment

We identified 68 evidence documents relevant to the question, of which we deemed 22 to be highly relevant. The highly relevant evidence documents include:

- two full systematic reviews;
- four non-systematic reviews that offered important insights; and
- 16 single studies.

We outline in narrative form below our key findings related to the question from highly relevant evidence documents, and based on experiences from other countries. A summary of the total number of evidence documents with relevance to each of the categories in the organizing framework is provided in Table 1, and a summary of findings from highly relevant evidence documents is provided in Table 2.

Box 1: Our approach

We identified evidence published from 2017 onwards (to capture any evidence related to recent outbreaks outside Africa) addressing the question by searching Health Systems Evidence (HSE), Health Evidence, ACCESSSS, PROSPERO (review protocols and registered titles) and PubMed on 24 May 2022. We identified jurisdictional experiences by hand searching government and stakeholder websites. We selected 11 countries (Australia, Belgium, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, United Kingdom, and the United States) that are non-endemic for monkeypox and that have had recent documented cases.

We searched for guidelines, full systematic reviews (or review-derived products such as overviews of systematic reviews), rapid reviews, protocols for systematic reviews, and titles/questions for systematic reviews or rapid reviews that have been identified as either being conducted or prioritized to be conducted.

We appraised the methodological quality of full systematic reviews and rapid reviews that were deemed to be highly relevant using AMSTAR. Note that quality appraisal scores for rapid reviews are often lower because of the methodological shortcuts that need to be taken to accommodate compressed timeframes. AMSTAR rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. It is important to note that the AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to systematic reviews pertaining to delivery, financial or governance arrangements within health systems or to broader social systems. We appraised the quality of the highly relevant guidelines using three domains in AGREE II (stakeholder involvement, rigour of development, and editorial independence) and classified guidelines as high quality if they were scored as 60% or higher on each domain.

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

Additional detail about experiences from other countries and from Canadian provinces and territories are provided in Tables 3 and 4. A detailed summary of our methods is provided in Appendix 1, the full list of included evidence documents (including those deemed of medium and low relevance) in Appendix 2, and hyperlinks for documents excluded at the final stage of reviewing in Appendix 3. Note that we summarized key points from each of the highly relevant evidence documents in Appendix 2, but only the title and the URL are listed for those deemed to be medium or low relevance.

Key findings from highly relevant evidence sources

Key findings from the highly relevant evidence documents are summarized below according to each of the categories in the organizing framework. Both full systematic reviews we identified were conducted recently ([2018](#) and [2020](#)), of medium quality, and are focused on what is known about the epidemiology of monkeypox outbreaks.

Biology

In terms of biology, we found that:

- [monkeypox is a zoonotic disease caused by the monkeypox virus](#) (MPXV), which is a member of the orthopoxvirus genus; and
- the [virus falls into two distinct strains](#), based on genetic, geographic, and phenotypic variation, these being the West African and the Congo Basin groups, with defined epidemiological and clinical differences.

Epidemiology (including transmission)

In terms of epidemiology (including transmission), we found general consensus in the two medium-quality systematic reviews and the single studies identified on transmission pathways for monkeypox. Transmission is noted as occurring from animals-to-humans and humans-to-humans, including through respiratory droplets and contact with body fluids, infected materials such as bedsheets, and skin lesion of an infected person. Human-to animal transmission has not been reported. Moreover, animal reservoirs play an important role in the transmission of monkeypox to humans, with monkeypox largely found in rodents and detected in squirrels, rats, mice and monkeys.

Most epidemiological case reports focused on transmission in African countries and point to possibly new and widespread zoonotic reservoirs of the monkeypox virus. In addition, the average age of monkeypox cases is increasing, presumably as a result of decreasing immunity that was provided by the era of routine smallpox vaccination.

Prevention and control

In terms of prevention and control, we found that:

- most confirmed monkeypox cases are in individuals born after the discontinuation of the smallpox vaccination campaign, likely reflecting a lack of cross-protective immunity provided by the vaccine;
- prevention measures for animal-to-human transmission include limiting contact with rodents and primates, limiting direct exposure to blood and inadequately cooked meat, and using personal protective equipment (e.g., disposable gowns and gloves, full facepiece respirators, face shields or gloves) when handling potential animal reservoir species;

- prevention measures for human-to-human transmission include avoiding close contact with anyone infected and healthcare providers using personal protective equipment when treating infected patients;
- public-health measures such as case isolation, contact tracing, avoiding contact with animals or materials suspected of being infected, use of personal protective equipment and good hand-hygiene practices, remain the best measures for preventing and controlling human monkeypox;
- a [single study on the response to a monkeypox outbreak](#) noted the establishment of a makeshift isolation ward for case management by a hospital-based monkeypox response team with the provision of infection and control resources, which:
 - identified challenges with some healthcare workers being reluctant to participate in the outbreak and with some avoiding suspected patients, and with patients and their family members experiencing stigma and discrimination and some refusing isolation, and
 - found that continued training and a collaborative approach with all involved stakeholders was able to address some of these challenges and eventually lead to successful containment of the outbreak; and
- a [study examining thresholds used to trigger a public-health response to monkeypox](#) identified three statistical thresholds (Cullen, c-sum, and a World Health Organization (WHO) method based on monthly incidence of cases), which concluded that:
 - using signals detected by a single method may be inefficient and overly simplistic for triggering public action for monkeypox, and instead, an alternative response algorithm was proposed which integrates the WHO method as an objective threshold with contextual information about epidemiological and spatiotemporal links between suspected cases.

Clinical presentation

In terms of clinical presentation, we found that:

- monkeypox symptoms generally occur in three phases: 1) an incubation period of four to 21 days; 2) prodromal illness with signs including lymph node enlargement, headache, fever, back pain, myalgia, intense asthenia, pharyngitis, sweating, and malaise; and 3) followed by an exanthema phase that includes vesiculopustular rashes that appear within one to 10 days spread over the body;
- monkeypox is similar to smallpox but generally less severe;
- case fatality rates range from around 1% to 10%, and occur mostly in young adults and children, especially those with immunosuppression; and
- complications include secondary bacterial infections, respiratory distress, broncho-pneumonia, encephalitis, corneal infection with vision loss, gastrointestinal involvement, vomiting, and diarrhea with dehydration.

Diagnosis

In terms of diagnosis, we found that:

- diagnosis of monkeypox can occur through genetic methods (i.e., PCR or RT-PCR), phenotypic methods based on clinical diagnosis, immunological methods including IgG and IgM antibody detection and immunohistochemistry for viral antigen detection, and electron microscopy;
- optimal clinical specimens for laboratory analyses include those from skin lesions, exudate, or crusts stored in a dry, sterile tube (without viral transport media) and kept cold, and the collection of an oropharyngeal swab is encouraged; and
- analysis should be carried out using electron microscopy through polymerase chain reaction.

Prognosis

In terms of prognosis, a [single study of 40 cases of monkeypox](#) from September 2017 to December 2018 in Nigeria found that 21 (52.5%) developed one or more complications including (in order of frequency) secondary bacterial infection, gastroenteritis, sepsis, bronchopneumonia, encephalitis, keratitis, and premature rupture of membrane at 16 weeks' gestation and resultant intrauterine fetal death. The same study found that:

- patients with HIV type 1 co-infection were significantly more likely to have larger skin rashes, genital ulcers, secondary bacterial infection, and longer duration of illness;
- five (12.5%) of the cases died; and
- sequelae observed amongst 18 patients discharged from hospital and seen at follow-up included hyperpigmented atrophic scars, hypopigmented atrophic scars, patchy alopecia, hypertrophic skin scarring, and contracture/deformity of facial muscles, with three of the 18 patients showing complete healing after eight weeks of follow-up.

Another [single study of 223 participants](#) found that hunting of non-human primates was associated with rash severity, but no association between rodent exposure and monkeypox rash severity.

[Another single study evaluated fetal outcomes in four pregnant women infected with monkeypox](#) and found that three of the four experienced fetal demise. The study indicated that this suggests that maternal monkeypox infection may have adverse consequences for the fetus without apparent correlation with severity of maternal disease.

Treatment

In terms of treatment, [a recent medium-quality systematic review](#) reported that monkeypox is primarily treated through supportive care, symptomatic management, and treatment of secondary bacterial infections. In addition, a [non-systematic review](#) reported that antivirals such as Tecovirimat, Cidofovir and Brincidofovir have shown efficacy in in vitro and animal studies, but their effectiveness in humans is unknown. The [same non-systematic review](#) found that:

- Brincidofovir may have an improved safety profile compared to Cidofovir;
- Cidofovir and Brincidofovir may be considered in severe cases of monkeypox; and
- human clinical trials of Tecovirimat suggested that the drug was safe and tolerable with only minor side effects.

In addition, [a single study of pregnant women infected with monkeypox](#) in the Democratic Republic of Congo noted that during hospitalization, pregnant women received antibiotics (amoxicillin, chloramphenicol via eye drops, and erythromycin, as well as gentamycin, if necessary) for prevention or control of bacterial superinfection, paracetamol and papaverine were given as analgesics, metronidazole and mebendazole were administered for giardiasis and other intestinal parasitic infections, and quinine as given for malaria.

Key findings from the jurisdictional scan

Biology

Countries and provinces examined characterize monkeypox as a viral zoonotic disease caused by an orthopoxvirus (MPXV).

Epidemiology (including transmission)

Human monkeypox was first identified in the Democratic Republic of the Congo in 1970 and has since been reported across several other central and western African countries, and occasionally in countries outside of Africa including in the United States (47 cases in 2003 and one in 2021), the United Kingdom (four cases in 2018-19 and three in 2021), Israel (one case in 2018), and Singapore (one case in 2019). As of Wednesday 25 May 2022, there were 219 confirmed cases outside of countries in which monkeypox is endemic. While cases have been confirmed in several countries in Europe and North America, 51 of these confirmed cases were reported in Madrid, Spain and 78 cases of monkeypox were confirmed in the U.K. between 7-24 May 2022. As of 25 May 2022, 16 cases have been confirmed in Canada.

Monkeypox can spread to humans via animals (rodents and primates) as well as other humans and contaminated objects such as bedding. Animal-to-human transmission may occur by bite or scratch, bushmeat preparation, direct contact with body fluids or lesion material, or indirect contact with lesion material, such as through contaminated bedding. Human-to-human transmission is thought to generally occur through large respiratory droplets requiring prolonged face-to-face contact. An infected pregnant woman may also pass monkeypox on to her developing fetus.

Prevention and control

Broadly, jurisdictions align with the recommendations from the [U.S. CDC](#), which recommends that the following measures be taken to prevent infection with monkeypox virus:

- avoid contact with animals that could harbour the virus (including animals that are sick or that have been found dead in areas where monkeypox occurs);
- avoid contact with any materials, such as bedding, that has been in contact with a sick animal;
- isolate infected patients from others who could be at risk for infection;
- practise good hand hygiene after contact with infected animals or humans (e.g., washing your hands with soap and water or using an alcohol-based hand sanitizer); and
- use personal protective equipment (PPE) when caring for patients.

The countries reviewed also noted that high-risk contacts such as sexual partners, family members, and others in contact with skin blisters should also quarantine. If they take a test that has a negative result, they may end their quarantine and if the result is positive, they should continue isolating. Across jurisdictions, recommended isolation periods include periods of at least 21 days or others that recommend until the scabs have fallen off and their skin is completely healed. Belgium was the first country to announce a mandatory 21-day isolation period for individuals infected with monkeypox.

Many jurisdictions have source and contact-tracing measures in place in the event of a confirmed case. The UK Health Security Agency produced a [monkeypox contact-tracing classification and vaccination matrix](#) to help guide follow-up and vaccination advice for individuals who have had varying levels of exposure risk with confirmed cases of monkeypox. The [Ontario Monkeypox Investigation Tool](#) was created to record patient information and prevent future illness caused by monkeypox. Additionally, some jurisdictions are buying smallpox vaccines to help prevent monkeypox. For example, Germany ordered 40,000 smallpox vaccine doses as a preventive measure and the U.K. has purchased supplies of Imvanex (a smallpox vaccine) to be offered to close contacts of those diagnosed with monkeypox to reduce their risk of symptomatic infection and severe illness.

There are some discrepancies across countries about the classification of the virus, for example, with the U.K. classifying monkeypox as an Advisory Committee on Dangerous Pathogens (ACDP) Hazard Group 3 pathogen, which must be handled at full containment level 3, and Spain classifying smallpox samples as category B using standard precautions for their transport.

Clinical presentation

The incubation period can range from five to 21 days. At the onset of the infection, symptoms are described as mild and include fever, headache, muscle ache, swollen lymph nodes, chills, and fatigue. Between one and five days after the onset of fever, a rash develops, often starting on the face and then spreading to other parts of the body with the rash tending to be more concentrated on the face and extremities than on the trunk. Generally, the disease affects the face (in 95% of cases); the palms of the hands and soles of the feet (in 75% of cases); the oral mucosa (in 70% of cases); the genitalia (30%); and the conjunctiva and cornea (20%). However, in most of the known recent cases in Europe, the rash has started around the pubic or anus region before spreading to the rest of the body.

The [B.C. Centre for Disease Control](#) maintains a webpage about monkeypox for healthcare providers with information about clinical presentation, transmission, management of suspected cases (including diagnosis and testing), infection prevention and control, and treatment.

Diagnosis

Diagnosis of the monkeypox virus primarily occurs first through clinical assessment and then confirmed through laboratory testing of biological specimens. Clinicians can recognize potential monkeypox infection based on the similarity of its clinical course to that of smallpox. The main feature that distinguishes infection with monkeypox from that of smallpox is the development of swollen lymph nodes (lymphadenopathy). The spectrum of monkeypox disease ranges from mild to severe and fatal. The virus can be detected using polymerase chain reaction (PCR) and the particles can further be detected through an electron microscope. The UK Health Security Agency has produced guidance for [collecting, submitting, and processing of samples](#) for the diagnosis of monkeypox.

Prognosis

Most monkeypox cases are mild and the infected person will recover within a few weeks. Although monkeypox is generally mild, it has been reported to be potentially more severe in children and immunocompromised individuals, as there is the possibility of superinfections of skin lesions or further complications arising from existing respiratory, digestive, ophthalmological, or neurological disorders. Complications may include secondary bacterial infections, bronchopneumonia, sepsis, encephalitis, and corneal infection with subsequent loss of vision. The severity of illness can depend upon the initial health of the individual, the route of exposure, and the strain of the infecting virus (West African versus Central African virus genetic groups, or clades).

Treatment

All jurisdictions highlight that treatment for monkeypox is mainly supportive. However, while most patients recover well with only supportive care, some patients may need pain medication, intravenous fluids, and viral medications for severe cases. Recently, the European Union approved Tecovirimat to help treat monkeypox infections (but its availability is currently limited). The U.S.

CDC lists antivirals Cidofovir, Brincidofovir and Tecovirimat as possible treatments for severe cases of monkeypox, but that their clinical effectiveness in humans has not yet been confirmed. Additionally, several countries note that smallpox vaccines, antivirals, and vaccinia immune globulin may be used during the first few days for someone who may have been infected as a preventive measure to help control outbreaks.

Table 1: Overview of topics related to monkeypox addressed by all included evidence documents

Type of evidence document	Total*	Biology	Epidemiology (including transmission)	Infection and control	Clinical presentation	Diagnosis	Prognosis	Treatment
Guidelines	0	-	-	-	-	-	-	-
Full systematic reviews	2	-	2	-	-	-	-	-
Rapid reviews	0	-	-	-	-	-	-	-
Non-systematic reviews	6	4	5	4	4	4	2	3
Protocols for reviews or rapid reviews that are underway	0	-	-	-	-	-	-	-
Titles/questions for reviews that are being planned	0	-	-	-	-	-	-	-
Single studies	60	12	29	14	15	8	6	12

*Some documents were tagged in more than one category so the column total does not match the total number of documents.

Table 2: Key findings from highly relevant documents about monkeypox organized by the framework domains

Organizing framework domain	Key findings from highly relevant documents
Biology	<ul style="list-style-type: none"> • A medium-quality systematic review and a non-systematic review reported that monkeypox is a zoonotic disease caused by the monkeypox virus (MPXV) which is a member of the orthopoxvirus genus (6/11 AMSTAR rating; literature last searched 15 August 2018; Published 12 November 2020) • A medium-quality systematic review and non-systematic review described that the monkeypox virus falls into two distinct strains, based on genetic, geographic, and phenotypic variation, these being the West African and the Congo Basin groups, with defined epidemiological and clinical differences (6/11 AMSTAR rating; literature last searched 15 August 2018; Published December 2019)
Epidemiology (including transmission)	<ul style="list-style-type: none"> • A medium-quality systematic review reported that outside of the Democratic Republic of Congo (DRC), there has been a notable increase in number of individual monkeypox outbreak reports between 2010 and 2018, particularly in the Central African Republic, but the authors noted that this does not necessarily translate to an increase in annual cases over time in these areas <ul style="list-style-type: none"> ◦ In Nigeria, geographical patterns of infections suggest a possible new and widespread zoonotic reservoir (6/11 AMSTAR rating; literature last searched 15 August 2018) • A low-quality systematic review reported that from 2009-2019 there have been almost 20,000 suspected or confirmed cases of monkeypox, and of those cases, one was in Israel in 2018, three in the U.K. in 2018 and one in 2019, and one in Singapore in 2019 <ul style="list-style-type: none"> ◦ The median age at presentation has increased from four-to-five years old from 1970-1989 to 21 years in 2010-2019, with cases outside of Africa even higher and occurring most frequently in adult males ◦ The authors hypothesize that this increase may be due to the cessation of smallpox vaccinations, which provided some cross-protection against monkeypox (4/11 AMSTAR rating; literature last searched 7 September 2020) • A non-systematic review reported that the two possible means of MPXV transmission are animals-human transmission and human-human transmission, and respiratory droplets and contact with body fluids, contaminated patient's environment or items, skin lesion of an infected person associated with inter-human transmission (Published 12 November 2020) <ul style="list-style-type: none"> ◦ Animal-to-human transmission occurs through direct contact with the above viral hosts or by direct contact with blood ◦ Human-to-animal transmission has not been reported • A non-systematic review reported that the frequency and geographic distribution of human monkeypox cases across West and Central Africa have increased in recent years <ul style="list-style-type: none"> ◦ Monkeypox is largely found in rodents and has been detected in squirrels, rats, mice and monkeys ◦ Indirect or direct contact with live or dead animals is assumed to be the main source of human monkeypox infections ◦ Secondary human-to-human transmission is considered common and presumably occurs through respiratory droplets or indirect or direct contact with body fluids, lesion material and contaminated surfaces or other material (Published December 2019) • A non-systematic review indicated that transmission to humans is primarily by exposure to animal reservoirs (primary zoonotic transmission), such as squirrels (Published April 2019)

	<ul style="list-style-type: none"> • A non-systematic review reported that the current evidence indicates that an outbreak is caused by multiple sources emerging into the human population, and is not sustained by human-to-human transmission; however, most cases are reported individually which prevents an accurate picture of the overall transmission <ul style="list-style-type: none"> ○ There are current knowledge gaps in the epidemiology, host reservoir, emergence, transmission, pathogenesis, and prevention of monkeypox • A single study described an imported case of monkeypox from Nigeria to the United Kingdom, whereby secondary transmission occurred within the family <ul style="list-style-type: none"> ○ After arrival, case one developed a vesicular lesion, day 19 an 18-month-old child within the family developed lesions, and by day 33, an adult member developed a vesicular rash and confirmed with monkeypox through PCR testing ○ 30 contacts were identified for active surveillance as they had direct exposure to broken skin or mucous membrane of a symptomatic patient (Published 21 August 2021) • A single study found that in the Democratic Republic of the Congo, the incidence of monkeypox from 2011-2015 was lower among those presumed to have received smallpox vaccination than among those presumed unvaccinated <ul style="list-style-type: none"> ○ The highest incidence was among 10-to-19-year-old males, the cohort reporting the highest proportion of animal exposures (37.5%) ○ The authors concluded that the increase in the incidence of monkeypox might be linked to declining immunity provided by smallpox vaccination (Published 4 June 2021) • A single study used historical data from the Democratic Republic of the Congo to estimate the reproduction number (R) and basic reproduction number (R0) of smallpox and monkeypox in a population with imperfect immunity <ul style="list-style-type: none"> ○ With data from 2011-2012 that indicate a 60% population immunity against orthopoxvirus species, the R value for monkeypox was calculated to be 0.85 (UI: 0.51-1.25) (Published 8 July 2020) • A single study described the transmission of monkeypox virus from an investigation that Public Health England (PHE) conducted of two unrelated cases of monkeypox that affected travellers returning from Nigeria <ul style="list-style-type: none"> ○ Transmission of monkeypox occurred between the second patient to a healthcare worker, most likely the only exposure risk identified during assessment of the infected healthcare worker was the changing of potentially contaminated bedding, when patient 2 had multiple skin lesions, but before a diagnosis of monkeypox had been considered (Published April 2020) • A single study examined the association between exposure to rodents and non-human primates with rash severity amongst confirmed cases from the monkeypox surveillance program in the Democratic Republic of the Congo <ul style="list-style-type: none"> ○ The authors reported no association found between rodent exposure and monkeypox rash severity (Published 24 December 2019) • A single study described the seroprevalence of orthopoxviruses amongst employees of a primate sanctuary and residents of nearby villages in Cameroon <ul style="list-style-type: none"> ○ Forty-three participants (34.4%) were IgG positive for anti-orthopoxvirus antibodies; however, amongst those born after the era of routine smallpox vaccination only four (6.3%) were positive for anti-orthopoxvirus antibodies
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	<ul style="list-style-type: none"> ○ The authors concluded that presence of anti-orthopoxvirus antibodies in individuals born after the era of smallpox vaccination suggests the possibility of asymptomatic circulation of an orthopoxvirus (which was most likely monkeypox) in human populations (Published 25 November 2019) ● A single study reported the epidemiological features of the 2017 to 2018 human monkeypox outbreak in Nigeria, the largest documented human outbreak of the west African strain of the monkeypox virus <ul style="list-style-type: none"> ○ Data was collected with a standardized form based on a case definition of human monkeypox from previously established guidelines ○ Diagnosis of the human monkeypox virus infection was confirmed by viral identification with real-time PCR and detection of antibodies ○ The results showed that 122 confirmed or probable cases of human monkeypox was recorded in 17 states of Nigeria, infecting individuals from the ages of two to 50 years ○ All patients had rashes on all parts of the body, fever, headaches, and lymphadenopathy ○ The results suggest endemicity of monkeypox virus in Nigeria, with some evidence of human-to-human transmission (Published August 2019) ● A single study reported an outbreak investigation involving human monkeypox cases from four districts (Impfondo, Betou, Dongou, and Enyelle) in the Likouala department of the Republic of the Congo <ul style="list-style-type: none"> ○ The results showed that there were no epidemiologic links between cases from different districts, and all hypothesized human-to-human transmission events appeared to have been contained within the individual districts ○ There was no evidence suggesting that the virus was introduced from neighbouring countries ○ The authors noted some challenges associated with the remote regions of the districts, such as limited health and transportation infrastructure, absence of specimen collection supplies, and a well-functioning cold chain, that would have resulted in inconsistent and incomplete reporting (Published February 2019) ● A single study found that rope squirrels shed large quantities of the virus and for long periods, supporting the hypothesis that they play a potential role in monkeypox virus transmission to humans and other animals in the Central African region (Published 21 August 2017)
Clinical presentation	<ul style="list-style-type: none"> ● A non-systematic review reported that monkeypox symptoms can occur in three phases: 1) an incubation period of four to 21 days; 2) prodromal illness with signs including lymph node enlargement, headache, fever, back pain, myalgia, intense asthenia, pharyngitis, sweating and malaise; and 3) followed by an exanthema phase that includes vesiculopustular rashes that appear within one to 10 days spread over the body (Published 12 November 2020) ● A non-systematic review described that monkeypox is similar to smallpox but generally less severe (Published December 2019) <ul style="list-style-type: none"> ○ Incubation period is estimated at five to 21 days, and symptoms and signs at two to five weeks ○ The illness begins with nonspecific symptoms and signs including fever, chills, headaches, lethargy, asthenia, lymph node swelling, back pain, and myalgia, followed by rashes of varying size that appear first on the face then across the body, hands, legs, and feet ○ Complications such as secondary bacterial infections, respiratory distress, broncho-pneumonia, encephalitis, corneal infection with vision loss, gastrointestinal involvement, vomiting, and diarrhea with dehydration

	<ul style="list-style-type: none"> ○ Case fatality rates have varied from 1% to 10% and occur mostly among young adults and children, especially those with immunosuppression ● A non-systematic review indicated that the clinical presentation of the monkeypox virus largely resembles that of smallpox, with an incubation period of seven to 17 days, and includes fever, muscle aches, backache, lymphadenopathy, followed by lesions and rashes all over the body (Published April 2019) ● A non-systematic review indicated that the clinical presentations of the monkeypox virus includes symptoms with skin and mucosal lesions which are difficult to distinguish from smallpox, and the infection starts with fever, headache, back pain, myalgia and asthenia followed by eruption of skin and mucosal lesions starting with the face (Published January 2019) ● A single study reported that a suspected monkeypox case was defined as an individual with a vesicular or pustular rash with deep-seated, firm pustules, and ≥ 1 of the following symptoms: fever preceding the eruption, lymphadenopathy (inguinal, axillary, or cervical), or pustules or crusts on the palms of the hands or soles of the feet (Published 4 June 2021) ● A single study described the clinical course and management of 40 hospitalized monkeypox cases during the 2017-2018 human monkeypox outbreak in Nigeria using retrospective records <ul style="list-style-type: none"> ○ The most common clinical features observed (in order) included skin rash, fever, lymphadenopathy, genital ulcers, body aches, headache, sore throat, pruritus, and conjunctivitis and photophobia ○ The most common first symptoms were rash and fever ○ Twenty-one (52.5%) of 40 cases developed one or more complications including (in order of frequency) secondary bacterial infection, gastroenteritis, sepsis, bronchopneumonia, encephalitis, keratitis, and premature rupture of membrane at 16 weeks' gestation and resultant intrauterine fetal death ○ Patients with HIV type 1 co-infection were significantly more likely to have larger skin rashes, genital ulcers, secondary bacterial infection, and longer duration of illness ○ Sequelae observed amongst 18 patients discharged from hospital and seen at follow-up included hyperpigmented atrophic scars, patchy alopecia, hypertrophic skin scarring, and contracture/deformity of facial muscles, with three of the 18 patients showing complete healing after eight weeks of follow-up (Published 15 October 2020)
Prevention and control	<ul style="list-style-type: none"> ● A non-systematic review noted that vaccination against smallpox provides cross-protection against other OPV species including MPXV (monkeypox) and many patients were born after the cessation of smallpox eradication program (Published 12 November 2020) ● A separate non-systematic review similarly highlighted that most confirmed monkeypox cases are younger than 40 years old, a population born only after the discontinuation of the smallpox vaccination campaign, possibly reflecting a lack of cross-protective immunity (Published December 2019) <ul style="list-style-type: none"> ○ Prevention measures for animal-to-human transmission include avoiding contact with rodents and primates, limiting direct exposure to blood and inadequately cooked meat, and using personal protective equipment when handling potential animal reservoir species ○ Prevention measures for human-to-human transmission include avoiding close contact with anyone infected and healthcare providers using personal protective equipment when treating infected patients

	<ul style="list-style-type: none"> • A non-systematic review highlighted that other key public-health measures, such as case isolation, contact tracing, avoiding contact with animals or materials suspected of being infected, use of personal protective equipment and good hand-hygiene practices, remain the best measures for preventing and controlling human monkeypox (Published April 2019) • A single study of an outbreak of monkeypox mentions the use of contact tracing and active surveillance of 30 contacts identified as having had direct exposure to broken skin or mucous membranes of a symptomatic patient (Published 21 August 2021) • A cross-sectional single study of strategies used, and challenges faced when responding to a monkeypox outbreak noted (Published 17 April 2019): <ul style="list-style-type: none"> ○ To respond to the outbreak, the hospital established a makeshift isolation ward for case management by a monkeypox response team and provided infection and control resources ○ Challenges included some healthcare workers being reluctant to participate in the outbreak with some avoiding suspected patients; stigma and discrimination experienced by patients and their family members; and refusal of isolation ○ Training was offered and using a collaborative approach among all involved stakeholders addressed some of these challenges and eventually led to successful containment of the outbreak • A single study examining thresholds to trigger a public-health response to monkeypox identified three different statistical thresholds that were used: Cullen, c-sum, and a World Health Organization (WHO) method based on monthly incidence (20 December 2018) <ul style="list-style-type: none"> ○ The study concluded that using signals detected by a single method may be inefficient and overly simplistic for triggering public-action for monkeypox ○ Instead, a response algorithm is proposed which integrates the WHO method as an objective threshold with contextual information about epidemiological and spatiotemporal links between suspected cases
Diagnosis	<ul style="list-style-type: none"> • A non-systematic review highlighted that diagnosis of monkeypox can occur through genetic methods (i.e., PCR or RT-PCR), phenotypic methods based on clinical diagnosis, immunological methods including IgG and IgM antibody detection and immunohistochemistry for viral antigen detection, and electron microscopy (Published 12 November 2020) <ul style="list-style-type: none"> ○ For diagnosis, optimal clinical specimens for laboratory analyses include those from skin lesions, exudate, or crusts stored in a dry, sterile tube (without viral transport media) and kept cold • A single study noted that that a confirmed monkeypox case requires detection of Orthopoxvirus or MPXV DNA with real-time polymerase chain reaction (PCR) or isolation of MPXV in culture from ≥ 1 specimen (Published 4 June 2021) <ul style="list-style-type: none"> ○ swab eluates, crust homogenates, or blood from suspected cases were used to test for monkeypox infection
Prognosis	<ul style="list-style-type: none"> • A single study of 40 monkeypox cases found that 21 (52.5%) developed one or more complications including (in order of frequency) secondary bacterial infection, gastroenteritis, sepsis, bronchopneumonia, encephalitis, keratitis, and premature rupture of membrane at 16 weeks' gestation and resultant intrauterine fetal death (published 15 October 2020) <ul style="list-style-type: none"> ○ Five (12.5%) of the cases died ○ Patients with HIV type 1 co-infection were significantly more likely to have larger skin rashes, genital ulcers, secondary bacterial infection, and longer duration of illness ○ Sequelae observed amongst 18 patients discharged from hospital and seen at follow-up included hyperpigmented atrophic scars, patchy alopecia, hypertrophic skin scarring, and contracture/deformity of facial muscles; three of the 18 patients showed complete healing after eight weeks of follow-up

	<ul style="list-style-type: none"> • A cross-sectional single study of 223 participants found that hunting of non-human primates was associated with rash severity in both unadjusted and adjusted models (OR= 2.78 (95% CI: 1.18, 6.58)), while exposure to non-human primates was associated with rash severity only in an unadjusted model (published 24 December 2019) <ul style="list-style-type: none"> ◦ There was no association found between rodent exposure and monkeypox rash severity • In an observational single study of fetal outcomes of four pregnant women infected with monkeypox, three of four experienced fetal demise (17 October 2017) <ul style="list-style-type: none"> ◦ The study concluded that maternal MPXV infection may have adverse consequences for the fetus without apparent correlation with severity of maternal disease
Treatment	<ul style="list-style-type: none"> • A non-systematic review noted that monkeypox is primarily treated through supportive care, symptomatic management, and treatment of secondary bacterial infections (Published December 2019) • A non-systematic review highlights that antivirals such as Tecovirimat, Cidofovir and Brincidofovir have shown efficacy in in vitro and animal studies, but their effectiveness in humans is unknown (Published 12 November 2020) <ul style="list-style-type: none"> ◦ Cidofovir and Brincidofovir may be considered in severe cases of monkeypox ◦ Brincidofovir may have an improved safety profile compared to Cidofovir ◦ Human clinical trials of Tecovirimat suggested that the drug was safe and tolerable with only minor side effects • A non-systematic review noted that the recent development of Tecovirimat (and its licence in Nigeria) as an antipoxvirus cure is an important achievement in antiviral therapy (Published April 2019) • A single study examining monkeypox outbreaks in Africa concluded that robust disease-surveillance systems with initial and long-term financial and human resource investment are required to stop the spread of monkeypox (published 16 March 2018) <ul style="list-style-type: none"> ◦ Coordination of interventions and routine sharing of information between human and wildlife sectors is necessary because monkeypox is a zoonotic disease • A single study of pregnant women infected with monkeypox in the Democratic Republic of Congo noted that during hospitalization, pregnant women received antibiotics (amoxicillin, chloramphenicol via eye drops, and erythromycin, as well as gentamycin, if necessary) for prevention or control of bacterial superinfection, paracetamol and papaverine were given as analgesics, metronidazole and mebendazole were administered for giardiasis and other intestinal parasitic infections, and quinine as given for malaria (17 October 2017)

Table 3: Experiences in other countries related to available evidence about monkeypox

Country	Summary of experiences
Australia	<p>Biology</p> <ul style="list-style-type: none"> The government of Australia characterizes monkeypox as a viral zoonotic self-limited disease with symptoms lasting two to four weeks <p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> The government of Australia reported its first case on 20 May 2022 from an individual returning from the United Kingdom The government of Australia indicates that human-to-human transmission can occur through close contact with large lesions on the skin, typically around the head and neck, body fluids (including respiratory droplets), and contaminated materials <ul style="list-style-type: none"> The government of Australia noted that transmission can likely occur between sexual partners due to intimate contact with infectious skin lesions <p>Prevention and control</p> <ul style="list-style-type: none"> The government of Australia recommends medical advice for those who have recently travelled overseas or been in contact with a case in Australia The New South Wales government recommends the following prevention measures: 1) self-isolation until rash is fully resolved; 2) proper hand hygiene; 3) use of PPE around people infected with monkeypox; and 4) avoid contact with materials from a person infected with monkeypox (e.g., bedding) <p>Clinical presentation</p> <ul style="list-style-type: none"> The government of Australia indicates that the incubation period is between six and 13 days <ul style="list-style-type: none"> Symptoms during one to five days include fever, rash, and swelling of lymph nodes A rash usually occurs within one to three days around the face, arms, and legs after appearance of a fever <p>Diagnosis</p> <ul style="list-style-type: none"> The government of Australia indicates that monkeypox is confirmed with laboratory testing and clinical assessment <p>Treatment</p> <ul style="list-style-type: none"> The New South Wales government described that the disease is mild, but some patients may need pain medication, intravenous fluids, and viral medications for severe cases
Belgium	<p>Biology</p> <ul style="list-style-type: none"> Monkeypox is zoonotic disease caused by an orthopoxvirus <p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> An individual may be infected with Monkeypox if they come into contact with bodily fluids, mucous membranes, saliva droplets, and contaminated surfaces (e.g., bedding, towels, linen) of an infected individual Transmission of Monkeypox can also occur from infected animals through direct contact with blood or a bite <p>Prevention and control</p> <ul style="list-style-type: none"> Belgium was the first country to announce a mandatory 21-day quarantine period for individuals infected with Monkeypox

	<p>Clinical presentation</p> <ul style="list-style-type: none"> • The most common symptoms that appear after infection are fever, muscle aches, and a headache, which are usually followed by skin lesions (blisters and lumps) appearing over the entire body • Rashes on the palms of the hands and soles of the feet are a characteristic of the disease <p>Diagnosis</p> <ul style="list-style-type: none"> • As of 25 May 2022, Belgium has four confirmed cases of Monkeypox • The Institute for Tropical Medicine (ITM) located in Antwerp, Belgium has been permitted to conduct polymerase chain reaction (PCR) tests to detect Monkeypox, and to use samples of the vesicles and scabs on the skin for analysis <p>Prognosis</p> <ul style="list-style-type: none"> • The incubation period is typically between six and 13 days, but it can range anywhere from five to 21 days • The disease is usually mild, with the illness lasting two to four weeks <p>Treatment</p> <ul style="list-style-type: none"> • Currently, there are no approved treatments for Monkeypox, however, individuals typically recover on their own after a few weeks
France	<p>Biology</p> <ul style="list-style-type: none"> • Monkeypox is a rare viral infectious disease caused by an orthopoxvirus <p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> • The primary mode of disease transmission is from rodent-to-human, however, it can also be transmitted from human-to-human through direct contact with skin lesions, mucous membranes, respiratory droplets (which require prolonged face-to-face contact), and contaminated surface environments (e.g., bedding, clothes, dishes, and linen) of infected individuals <p>Prevention and control</p> <ul style="list-style-type: none"> • Currently, it is recommended that infected individuals complete a full isolation period of three weeks until the disappearance of all the scabs • The infected individual is contagious upon the appearance of their first symptom(s) <p>Clinical presentation</p> <ul style="list-style-type: none"> • An infection caused by the Monkeypox virus initially presents with a fever, headaches, body aches, and asthenia, which is followed by the appearance of fluid-filled blistering rashes that eventually dry out over time and leave behind a scab and scar • The blistering rashes typically appear on the face, hands (palms), and feet (soles), while the mouth, genital area, and lymph nodes can all be affected too <p>Diagnosis</p> <ul style="list-style-type: none"> • As of 24 May 2022, there have been five confirmed cases of Monkeypox in France with three reported in Ile-de-France, one reported in Auvergne-Rhône-Alpes and one reported in Occitanie <p>Prognosis</p> <ul style="list-style-type: none"> • The incubation period of the disease can range from five to 21 days, with the initial fever lasting anywhere from one to three days • The disease is reportedly more severe in children and immunocompromised individuals, as there is the possibility of superinfections of skin lesions or further complications arising from existing respiratory, digestive, ophthalmological, or neurological disorders

	<p>Treatment</p> <ul style="list-style-type: none"> It is reported that this disease tends to spontaneously heal on its own, with the majority of individuals recovering within two to four weeks
Germany	<p>Biology</p> <ul style="list-style-type: none"> Monkeypox is an infectious disease caused by the monkeypox virus orthopoxvirus simiae <p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> The primary mode of transmission of Monkeypox to humans is from rodents, however it can also be transmitted through close contact with an infected individual or contaminated surface(s) <p>Prevention and control</p> <ul style="list-style-type: none"> In conjunction with the Robert Koch Institute (RKI), the Ministry of Health (BMG) has put forth a recommendation to help assist federal states in responding to the Monkeypox outbreak, and a key feature of this recommendation includes ordering an isolation period of at least 21 days for infected individuals As a preventive measure, Germany has also ordered 40,000 smallpox vaccine doses <p>Clinical presentation</p> <ul style="list-style-type: none"> The symptoms include a fever, swollen lymph nodes, skin rashes, pain, and itching in the genital area <p>Diagnosis</p> <ul style="list-style-type: none"> On 19 May 2022, the first confirmed case of Monkeypox was reported in Germany As of 25 May 2022, there are five confirmed cases of Monkeypox in Germany The virus can be detected using polymerase chain reaction (PCR) and the particles can further be detected through an electron microscope <p>Prognosis</p> <ul style="list-style-type: none"> The incubation period is normally between six and 13 days, but it can range anywhere from five to 21 days Monkeypox cases are usually mild and people recover within the span of a few weeks, though there may be instances of severe cases that arise within the population <p>Treatment</p> <ul style="list-style-type: none"> Tecovirimat was recently approved in the European Union to help treat Monkeypox infections (however its availability is currently limited)
Italy	<ul style="list-style-type: none"> None identified
Netherlands	<p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> Monkeypox occurs mostly in West and Central Africa, mainly infecting rodents <ul style="list-style-type: none"> Monkeypox is described as a zoonosis (a disease that can be transmitted from animals to humans) The virus can enter through mucous membranes (mouth, nose, eyes) and open wounds, and can also be spread through droplets from blisters or from mouth and pharynx It cannot be spread through droplets floating in the air It is suspected that many people have been infected with monkeypox through contact among men who have sex with men

	<ul style="list-style-type: none"> ○ The variant currently in Europe is not particularly infectious, but there is a lack of understanding in how it has spread to those who are currently sick <p>Prevention and control</p> <ul style="list-style-type: none"> • According to the Government of the Netherlands, infected individuals must undergo isolation at home <ul style="list-style-type: none"> ○ High-risk contacts such as sexual partners, family members, and others in contact with the skin blisters should also quarantine ○ If they take a test and it is negative, they can end their isolation ○ If they are positive, they should continue isolating until no longer being infectious, and their skin is healed completely and the scabs have fallen off their skin • The Municipal Public Health Service will begin source and contact tracing if someone tests positive <p>Clinical presentation</p> <ul style="list-style-type: none"> • Symptoms are described as mild, including fever, headache, muscle ache, swollen lymph nodes, chills, and fatigue <ul style="list-style-type: none"> ○ One to three days later, an infected person will get a rash that starts on the face and appears on the rest of the body ○ The rash will start as spots that develop, which form scabs that fall off the skin in two to three weeks ○ In most cases, the rash started in the anus and pubic region before spreading to the rest of the body <p>Diagnosis</p> <ul style="list-style-type: none"> • The Netherlands confirmed the first cases of monkeypox on 20 May 2022, and there are currently 12 known cases in the country • The Health Minister designated monkeypox as a category A disease on 24 May 2022, meaning that doctors must report new or suspected cases immediately to prevent its spread <p>Treatment</p> <ul style="list-style-type: none"> • According to the National Institute of Public Health and the Environment, the current smallpox vaccine can be used during the first few days of possible infection, and can be used preventively in people at greater risk of infection
Portugal	<p>Biology</p> <ul style="list-style-type: none"> • The government of Portugal characterizes monkeypox as a disease that is transmitted through contact with infected animals, people, or contaminated materials, which is often rare and does not easily spread among humans <p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> • As of 18 May 2022, Portugal has reported five confirmed cases of monkeypox, with 20 more suspected cases <ul style="list-style-type: none"> ○ All cases were mild and among young men within Lisbon and Tagus Valley <p>Clinical presentation</p> <ul style="list-style-type: none"> • The government of Portugal indicated that individuals should seek medical attention if they have ulcerative lesions, rash, and enlarged lymph nodes
Spain	<p>Biology</p> <ul style="list-style-type: none"> • The Ministry of Health of Spain has developed a guideline for the management of Monkeypox, which defines monkeypox (MPXV) as a rare viral zoonotic disease <p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> • The first human cases were identified in the Democratic Republic of the Congo in 1970

	<ul style="list-style-type: none"> ○ While the majority of documented cases of MPXV have occurred in the Democratic Republic of the Congo, the number of cases in other West and Central African countries has increased during the last decade ● Since 2016, confirmed cases of MPXV have been reported in the Central African Republic, the Democratic Republic of the Congo, Liberia, Nigeria, the Republic of the Congo, and Sierra Leone, and several African countries in these regions are currently experiencing active outbreaks of MPXV ● Outside of Africa, cases of human MPXV infections have been documented in different countries: 47 cases in the United States in 2003 and one in 2021, four cases in the United Kingdom (U.K.) in 2018-19 and three in 2021, one case in Israel in 2018 and a case in Singapore in 2019 ● The Public Health Agency of Spain reported 51 cases of orthopoxvirus confirmed in Madrid, and 43 are under study ● Those diagnosis were confirmed after PCR tests carried out by the laboratory of the National Center for Microbiology (CNM) of the Carlos III Health Institute (ISCIII) <p>Prevention and control</p> <ul style="list-style-type: none"> ● The Government of Spain will buy vaccines and antivirals to treat monkeypox, and the Minister of Health announced that the government has already negotiated these acquisitions with the European Medicines Agency (EMA), which is the health emergency preparedness authority and responsible for making the IMvanex vaccine available ● Historically, smallpox vaccination has been shown to protect partially against MPXV <p>Clinical presentation</p> <ul style="list-style-type: none"> ● MPXV infection is usually a self-limited illness, and most people recover within several weeks, however, in some cases serious illness can occur ● The incubation period is six to 16 days, but can range from five to 21 days ● The classic initial clinical picture described until this outbreak usually includes fever, headache, muscle aches, lymphadenopathy, and fatigue ● Between one and five days after the onset of fever, a rash develops, often starting on the face and then spreading to other parts of the body with the rash tending to be more concentrated on the face and extremities than on the trunk ● The disease affects the face (in 95% of cases); the palms of the hands and soles of the feet (in 75% of cases); the oral mucosa (in 70% of cases); the genitalia (30%); and the conjunctiva and cornea (20%) ● Areas of erythema or hyperpigmentation of the skin around the lesions are usually seen ● The lesions can vary in size, the rash evolves sequentially from macules to papules, vesicles, pustules, and crusts that dry up and fall off ● In the first reported cases associated with this outbreak, genital and peri-oral lesions have been identified in a high number of cases ● Symptoms usually last from two to four weeks <p>Diagnosis</p> <ul style="list-style-type: none"> ● The clinical differential diagnosis that should be considered includes other exanthematous diseases that can present with a generalized pustular or vesicular eruption, such as smallpox (because of the risk that it could be an intentional event), chickenpox,
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	<p>herpes virus, eczema herpeticum, some enteroviruses (such as coxsackie or echovirus), measles, bacterial skin infections, scabies, syphilis, drug-associated allergies and some dermatological diseases</p> <ul style="list-style-type: none"> • Lymphadenopathy during the prodromal stage of the disease may be a clinical feature to distinguish MPXV from varicella or smallpox • The guideline developed by the Ministry of Health of Spain has recommended that samples to be obtained in a suspected case should be taken from the skin lesion (vesicular fluid, smear of vesicular lesions, exudates or scabs) • The skin lesion sample must be sent in virus transport medium and kept cold • If this sample is not available or additional studies are required, other samples may be used by contacting the National Institution of Microbiology in Spain in advance • Clinical samples are considered category B and, therefore, standard precautions are sufficient for transporting the samples <p>Prognosis</p> <ul style="list-style-type: none"> • The guideline for the management of monkeypox developed by the Ministry of Health of Spain has indicated that the number of injuries varies from a few to several thousand and, in severe cases, the lesions may coalesce until large sections of skin are shed • Severe cases occur most often among children, young adults, and immunocompromised persons, and are related to the degree of exposure to the virus and the vulnerability of the person • Complications may include secondary bacterial infections, bronchopneumonia, sepsis, encephalitis, and corneal infection with subsequent loss of vision • Its clinical presentation is milder than smallpox, and the case fatality rate for the West African clade has been documented to be around 1%, while for the Congo Basin clade it can be as high as 10% <p>Treatment</p> <ul style="list-style-type: none"> • Among three antivirals available, the Government of Spain has preferred Tecovirimat, which seems to present the best outcomes • The Government of Spain will join a centralized purchase under the terms agreed with the corresponding pharmaceutical company
Sweden	<p>Biology</p> <ul style="list-style-type: none"> • The Public Health Agency of Sweden defines monkeypox as a rare, sporadic species of the Orthopoxvirus that can be transmitted between animals and humans <ul style="list-style-type: none"> ◦ It has previously infected people in African rainforests where the reservoirs of the virus are primarily wild monkeys <p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> • The Public Health Agency of Sweden reported that the incubation period of monkeypox is usually six to 13 days, but can vary between five and 21 days <p>Clinical presentation</p> <ul style="list-style-type: none"> • Symptoms of monkeypox often include mild skin rashes and blisters that can spread to different parts of the body, as well as fever and swollen lymph nodes • If the virus is transmitted sexually, blisters on the genitals and around the anus can occur <p>Diagnosis</p> <ul style="list-style-type: none"> • Sweden confirmed its first case of monkeypox on 19 May 2022, and it is unknown how the person became infected

United Kingdom (U.K.)	<p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> Between 7 May 2022 and 24 May 2022, 78 cases of monkeypox have been confirmed in the U.K. The UK Health Security Agency has reported that a ‘notable proportion’ of cases reported to date have been among individuals who are gay or bisexual and men who have sex with men, and the agency is asking individuals in these groups to be aware of symptoms, especially if they recently had a new sexual partner <p>Prevention and control</p> <ul style="list-style-type: none"> The UK Health Security Agency has purchased supplies of Imvanex (a smallpox vaccine supplied by Bavarian Nordic) and is offering this vaccine to close contacts of those diagnosed with monkeypox to reduce their risk of symptomatic infection and severe illness <ul style="list-style-type: none"> High-risk contacts of confirmed cases are also being asked to isolate at home for up to 21 days The UK Health Security Agency notes that appropriate respiratory and contact precautions need to be taken and that scabs may be infectious, so bedding, clothing, and other articles need to be handled appropriately The monkeypox virus is classified as an Advisory Committee on Dangerous Pathogens (ACDP) Hazard Group 3 pathogen and the live virus must be handled at full containment level 3 Public Health England has produced a guidance document about environmental cleaning and decontamination with sections dedicated to healthcare and domestic settings The UK Health Security Agency has produced and updated recommendations for the use of pre- and post-exposure vaccination during a monkeypox incident <ul style="list-style-type: none"> This document contains background information regarding the Imvanex vaccine, recommendations regarding pre- and post-exposure vaccination, how to prioritize the vaccine stock, booster doses, and vaccine prescribing and administration The UK Health Security Agency has produced a monkeypox contact tracing classification and vaccination matrix to help guide follow-up and vaccination advice for individuals who have had varying levels of exposure risk with confirmed cases of monkeypox <p>Clinical presentation</p> <ul style="list-style-type: none"> The UK Health Security Agency has produced guidance regarding case definitions of possible, probable, and confirmed cases of monkeypox <p>Diagnosis</p> <ul style="list-style-type: none"> The UK Health Security Agency has produced guidance for collecting, submitting, and processing of samples for the diagnosis of monkeypox The rare and imported pathogens laboratory (RIPL) at the UK Health Security Agency Porton Down has been designated as the diagnostic laboratory for monkeypox <ul style="list-style-type: none"> Professionals are being asked to consult with the imported fever service before sending blood samples for testing Public Health England has produced a monkeypox guidance document for primary care which provides information on transmission, clinical features, patient assessment, and infection prevention and control <p>Treatment</p> <ul style="list-style-type: none"> The UK Health Security Agency notes that the smallpox vaccine, cidofovir, and Tecovirimat can be used to control outbreaks, but monkeypox treatment is mostly supportive
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United States (U.S.)	<p>Biology</p> <ul style="list-style-type: none"> According to the CDC, Monkeypox is a rare disease that is caused by infection with monkeypox virus, which belongs to the orthopoxvirus genus in the family Poxviridae <p>Epidemiology</p> <ul style="list-style-type: none"> The first human case of monkeypox was recorded in 1970 in the Democratic Republic of the Congo (DRC) during a period of intensified effort to eliminate smallpox Since then, monkeypox has been reported in people in several other central and western African countries: Cameroon, Central African Republic, Cote d'Ivoire, Democratic Republic of the Congo, Gabon, Liberia, Nigeria, Republic of the Congo, and Sierra Leone Transmission of monkeypox virus occurs when a person comes into contact with the virus from an animal, human, or materials contaminated with the virus On May 18, 2022, a U.S. resident tested positive for monkeypox after returning to the U.S. from Canada. As of May 18, 2022, no additional monkeypox cases have been identified in the U.S. The virus enters the body through broken skin (even if not visible), respiratory tract, or the mucous membranes (eyes, nose, or mouth) Animal-to-human transmission may occur by bite or scratch, bush meat preparation, direct contact with body fluids or lesion material, or indirect contact with lesion material, such as through contaminated bedding Human-to-human transmission is thought to occur primarily through large respiratory droplets <ul style="list-style-type: none"> Respiratory droplets generally cannot travel more than a few feet, so prolonged face-to-face contact is required Other human-to-human methods of transmission include direct contact with body fluids or lesion material, and indirect contact with lesion material, such as through contaminated clothing or linens <p>Prevention and control</p> <ul style="list-style-type: none"> In the United States, the two-dose Jynneos vaccine is licensed to prevent smallpox and specifically to prevent monkeypox According to the CDC, the following measures can be taken to prevent infection with monkeypox virus: <ul style="list-style-type: none"> Avoid contact with animals that could harbor the virus (including animals that are sick or that have been found dead in areas where monkeypox occurs) Avoid contact with any materials, such as bedding, that has been in contact with a sick animal Isolate infected patients from others who could be at risk for infection Practise good hand hygiene after contact with infected animals or humans (e.g., washing your hands with soap and water or using an alcohol-based hand sanitizer) Use personal protective equipment (PPE) when caring for patients <p>Clinical Presentation</p> <ul style="list-style-type: none"> In humans, the symptoms of monkeypox are similar to, but milder than, the symptoms of smallpox Monkeypox begins with fever, headache, muscle aches, and exhaustion
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- The main difference between symptoms of smallpox and monkeypox is that monkeypox causes lymph nodes to swell (lymphadenopathy) while smallpox does not
- The incubation period (time from infection to symptoms) for monkeypox is usually seven to 14 days, but can range from five to 21 days, and the illness typically lasts for two to four weeks
- The development of initial symptoms (e.g., fever, malaise, headache, weakness, etc.) marks the beginning of the prodromal period

Diagnosis

- [Clinicians can recognize potential monkeypox](#) infection based on the similarity of its clinical course to that of ordinary discrete smallpox
- A feature that distinguishes infection with monkeypox from that of smallpox is the development of swollen lymph nodes (lymphadenopathy)
- Swelling of the lymph nodes may be generalized (involving many different locations on the body) or localized to several areas (e.g., neck and armpit).
- Shortly after the prodrome, a rash appears
 - Lesions typically begin to develop simultaneously and evolve together on any given part of the body
 - The evolution of lesions progresses through four stages—macular, papular, vesicular, to pustular – before scabbing over and resolving
 - This process happens over a period of two to three weeks

Prognosis

- The severity of illness can depend upon the initial health of the individual, the route of exposure, and the strain of the infecting virus (West African versus Central African virus genetic groups, or clades).

Treatment

- Currently, [there is no proven, safe treatment for monkeypox virus infection](#)
- For purposes of controlling a monkeypox outbreak in the United States, smallpox vaccine, antivirals, and vaccinia immune globulin (VIG) can be used

Table 4: Experiences in Canadian provinces and territories related to available evidence about monkeypox

Province/territory	Summary of experiences
Pan-Canadian	<p>Biology</p> <ul style="list-style-type: none"> • According to the Government of Canada's website, monkeypox is a viral disease that can enter the body through broken skin, the respiratory tract, or the mucous membranes of the eyes, nose or mouth • The virus naturally occurs in Western and Central Africa, and the cessation of smallpox vaccination appears to have increased humans' susceptibility to severe monkeypox <p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> • Monkeypox can spread in three ways: 1) animals (e.g., rodents, primates) to humans; 2) person-to-person; and 3) through contaminated objects • Humans may also become infected by eating uncooked contaminated meat or through contact with body fluids from infected animals or humans • An infected pregnant women may also pass monkeypox on to her developing fetus • The virus is contagious from one to five days before the stage-two rash develops up until the scabs fall off and the skin heals <p>Prevention and control</p> <ul style="list-style-type: none"> • Since monkeypox primarily spreads through close contact, people can lower their risk of contracting monkeypox by maintaining physical distance and using frequent hand hygiene and respiratory hygiene, such as masking • In the coming days, the federal government will release updated guidance for infection prevention and control considering the recent confirmed cases of monkeypox <p>Clinical presentation</p> <ul style="list-style-type: none"> • The Government of Canada describes the symptoms of monkeypox in two stages that typically develop five to 21 days after exposure and last from two to four weeks: <ul style="list-style-type: none"> ◦ Stage one symptoms may include fever, headache, chills, swollen lymph nodes, muscle pain, back pain, joint pain, and exhaustion ◦ Stage two symptoms include a rash that develops on the face, extremities, or other parts of the body one to three days after the fever, and usually lasts between 14 and 21 days as it changes through different stages before it falls off as a scab <p>Diagnosis</p> <ul style="list-style-type: none"> • Diagnosis of monkeypox can be done by a healthcare provider, according to the Government of Canada's website <ul style="list-style-type: none"> ◦ Symptoms usually resolve within a few weeks and are often mild, but in rare cases, death can occur • As of 25 May 2022, there were 16 confirmed cases of monkeypox in Canada, a large increase from the first case count only a week prior <p>Prognosis</p> <ul style="list-style-type: none"> • Vaccination with the smallpox vaccine within four days and up to 14 days after initial contact with an infected monkeypox case can protect against monkeypox with greater than 85% efficacy

	<ul style="list-style-type: none"> Canada's Minister of Health, Jean-Yves Duclos announced on 24 May 2022 that Canada has a supply of Imvamune vaccines and therapeutics from the National Emergency Strategic Stockpile (NESS) that they will maintain as they work on rolling out a response plan <p>Treatment</p> <ul style="list-style-type: none"> Treatment for monkeypox is mainly supportive and there are no licensed antiviral drugs available to treat monkeypox According to a Montreal news report, the federal government will be sending vaccines and other “therapeutics” to Québec to help the province address the recent outbreak of monkeypox
British Columbia	<p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> As of 20 May 2022, there were no confirmed or suspected cases of monkeypox in British Columbia The British Columbia Centre for Disease Control maintains a webpage about monkeypox for healthcare providers with information about clinical presentation, transmission, management of suspected cases (including diagnosis and testing), infection prevention and control, and treatment <p>Prevention and control</p> <ul style="list-style-type: none"> The British Columbia Centre for Disease Control maintains a webpage about monkeypox for healthcare providers with information about clinical presentation, transmission, management of suspected cases (including diagnosis and testing), infection prevention and control, and treatment On 20 May 2022, the Provincial Health Officer of British Columbia issued a notice of duty to report all suspected cases of monkeypox as per the Reporting Information Affecting Public Health Regulation of the <i>Public Health Act</i> <p>Clinical presentation, diagnosis and treatment</p> <ul style="list-style-type: none"> The British Columbia Centre for Disease Control maintains a webpage about monkeypox for healthcare providers with information about clinical presentation, transmission, management of suspected cases (including diagnosis and testing), infection prevention and control, and treatment
Alberta	<p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> The Chief Medical Officer's 20 May 2022 notice for Alberta Health Services medical staff included a note about monkeypox <ul style="list-style-type: none"> The note included background information about monkeypox and reminded physicians about mandatory reporting for rare or emerging communicable diseases, and the need to notify the Medical Officer of Health regarding any suspected cases of monkeypox
Saskatchewan	<p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> Monkeypox does not spread easily from person to person and is primarily spread through prolonged face-to-face close contact, touching bodily fluids of a person who is sick with the disease, or from exposure to contaminated objects
Manitoba	<p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> Spread occurs when a person comes into close contact with an infected animal, human, or materials contaminated with the virus <p>Clinical presentation</p> <ul style="list-style-type: none"> Symptoms include fever, malaise, headache, backache, chills, weakness, and swollen lymph nodes

	<p>Diagnosis</p> <ul style="list-style-type: none"> • Manitoba is actively monitoring for monkeypox cases, although none have been identified yet <p>Treatment</p> <ul style="list-style-type: none"> • Treatment of monkeypox is mainly supportive, but in severe cases antivirals may be considered
Ontario	<p>Biology</p> <ul style="list-style-type: none"> • Monkeypox is an orthopoxvirus caused by the monkeypox virus (MPXV) <p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> • Monkeypox can be transmitted from animals to humans or by contact with infected lesions, skin scabs, body fluids, or respiratory secretions, and by being in contact with materials contaminated with the virus (clothing, bedding) <ul style="list-style-type: none"> ○ Human-to-human transmission of monkeypox is uncommon, but it may occur through respiratory droplets or contact with bodily fluids, skin lesions, and contaminated materials • There is possible transmission during the prodromal period (when early symptoms such as fever, malaise, and headache appear) and the potential for airborne transmission <p>Prevention and control</p> <ul style="list-style-type: none"> • The Ontario Monkeypox Investigation Tool was created to record patient information and prevent future illness caused by monkeypox • People can lower their risk of exposure by maintaining physical distance, frequently washing their hands, and wearing masks • Precautions should be taken until all scabs have fallen off and new skin is present <ul style="list-style-type: none"> ○ The airborne/droplet/contact precautions should be used: measures include airborne isolation rooms (AIR) with negative pressure ventilation, and when AIRs are not available, a patient can be placed in a single room with the door closed with a single toilet ○ If these measures are not feasible, patients should wear a medical mask and cover exposed lesions with clothing, sheets, or a gown, especially during transport across hospital facilities ○ Healthcare workers should wear a fit-tested and sealed N-95 mask, gloves, gown, and eye protection (face shield or goggles) ○ Soiled linens should be cleaned to prevent dispersal of microorganisms ○ Waste (dressings) should be disposed of according to facility-specific guidelines for infectious waste ○ Healthcare-grade cleaning agents with a Drug Identification Number (DIN) should be used <p>Clinical presentation</p> <ul style="list-style-type: none"> • Most people recover from monkeypox within two to four weeks, although severe illness can occur in some individuals <ul style="list-style-type: none"> ○ Symptoms include fever, chills, headache, myalgias, swollen lymph nodes in the neck and groin area, fatigue, and rashes (on face, limbs, palm of hands and soles of feet, mucous membranes like mouth and genitals) that follow one to three days after the onset of other symptoms ○ The Ontario Ministry of Health recorded other symptoms including chills/sweats, back pain/ache, sore throat/cough, coryza (inflammation of the mucous membrane of the nose), and distress • The incubation period averages seven to 14 days (range five to 21 days)

	<p>Diagnosis</p> <ul style="list-style-type: none"> On 19 May 2022, the Public Health Agency of Canada confirmed two cases of monkeypox <p>Treatment</p> <ul style="list-style-type: none"> Prior vaccination against smallpox provides some cross-protection to monkeypox
Québec	<p>Epidemiology (including transmission)</p> <ul style="list-style-type: none"> The Ministry of Health and Social Services in Quebec states that monkeypox contagiousness is limited compared to other viruses like the flu and COVID-19 because it is contracted by prolonged and close contact with an infected person <p>Clinical presentation</p> <ul style="list-style-type: none"> Infected people have mild symptoms, disappearing after 14-21 days, and do not require hospitalization Symptoms include fever, headache, muscle aches, back pain, swollen lymph nodes, chills, and fatigue Rashes also occur often on the face and may spread to other parts of body such as the genitals <p>Prevention and control</p> <ul style="list-style-type: none"> People who think they are infected should self-isolate at home, wear a mask, cover lesions, and avoid direct contact with others They should also monitor themselves for symptoms for 21 days and avoid sexual relations until 21 days after last contact <p>Diagnosis</p> <ul style="list-style-type: none"> The Ministry of Health and Social Services in Quebec confirmed the first two cases of monkeypox on 19 May 2022, and 20 other cases of genital ulcer lesions are under investigation As of 19 May 2022, all suspected cases have affected men who have sex with other men <p>Treatment</p> <ul style="list-style-type: none"> Antivirals could be an option, but their clinical usefulness must be evaluated before recommended
New Brunswick	<p>Prevention and control</p> <ul style="list-style-type: none"> New Brunswick is actively monitoring the monkeypox outbreak, but to date has no reported cases
Nova Scotia	<p>Prevention and control</p> <ul style="list-style-type: none"> Nova Scotia is actively monitoring the monkeypox outbreak, but to date has no reported cases
Prince Edward Island	<ul style="list-style-type: none"> None identified
Newfoundland and Labrador	<ul style="list-style-type: none"> None identified
Yukon	<ul style="list-style-type: none"> None identified
Northwest Territories	<ul style="list-style-type: none"> None identified
Nunavut	<ul style="list-style-type: none"> None identified

Wilson MG, Bhuiya A, Bain T, DeMaio P, Al-Khateeb S, Sharma K, Alam S, Mehta V, Soueidan S, Vélez CM, Loeb M, Lavis JN. Living evidence profile #6: What is the best-available evidence related to the monkeypox outbreak? Hamilton: McMaster Health Forum, 27 May 2022.

To help health- and social-system leaders as they respond to pressing challenges, the McMaster Health Forum prepares rapid evidence profiles like this one. This rapid evidence profile was commissioned by the Office of the Chief Science Officer, Public Health Agency of Canada. The opinions, results, and conclusions are those of the McMaster Health Forum and are independent of the funder. No endorsement by the Public Health Agency of Canada is intended or should be inferred.




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Appendix 1: Methodological details

We use a standard protocol for preparing living evidence profiles (LEP) to ensure that our approach to identifying research evidence as well as experiences from other countries and from Canadian provinces and territories are as systematic and transparent as possible in the time we were given to prepare the profile.

Identifying research evidence

For this LEP, we searched [ACCESSSS](#), [HealthEvidence](#), [Health Systems Evidence](#), and [PubMed](#) for:

- 1) guidelines (defined as providing recommendations or other normative statements derived from an explicit process for evidence synthesis);
- 2) full systematic reviews;
- 3) rapid reviews;
- 4) protocols for reviews or rapid reviews that are underway;
- 5) titles/questions for reviews that are being planned; and
- 6) single studies (when no guidelines, systematic reviews or rapid reviews are identified).

In each database we used the open search function for monkey pox OR monkeypox. In PubMed, we used the MeSH headings of monkeypox and monkeypox virus. All searches were limited to literature published from 2017 onwards to capture any evidence related to recent outbreaks outside Africa.

Each source for these documents is assigned to one team member who conducts hand searches (when a source contains a smaller number of documents) or keyword searches to identify potentially relevant documents. A final inclusion assessment is performed both by the person who did the initial screening and the lead author of the rapid evidence profile, with disagreements resolved by consensus or with the input of a third reviewer on the team. The team uses a dedicated virtual channel to discuss and iteratively refine inclusion/exclusion criteria throughout the process, which provides a running list of considerations that all members can consult during the first stages of assessment.

During this process we include published, pre-print and grey literature. We do not exclude documents based on the language of a document. However, we are not able to extract key findings from documents that are written in languages other than Chinese, English, French or Spanish. We provide any documents that do not have content available in these languages in an appendix containing documents excluded at the final stages of reviewing.

Identifying experiences from other countries and from Canadian provinces and territories

For each LEP, we collectively decide on what countries to examine based on the question posed. For other countries we searched relevant government and stakeholder websites. In Canada, we search websites from relevant federal and provincial governments, ministries and agencies (e.g., Public Health Agency of Canada).

While we do not exclude countries based on language. Where information is not available in English, Chinese, French or Spanish, we attempt to use site-specific translation functions or Google translate.

Assessing relevance and quality of evidence

We assess the relevance of each included evidence document as being of high, moderate or low relevance to the question. We then use a colour gradient to reflect high (darkest blue) to low (lightest blue) relevance.

Two reviewers independently appraised the quality of the guidelines we identified as being highly relevant using AGREE II. We used three domains in the tool (stakeholder involvement, rigour of development and editorial independence) and classified guidelines as high quality if they were scored as 60% or higher across each of these domains.

Two reviewers independently appraise the methodological quality of systematic reviews and rapid reviews that are deemed to be highly relevant. Disagreements are resolved by consensus with a third reviewer if needed. AMSTAR rates overall methodological quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. High-quality reviews are those with scores of eight or higher out of a possible 11, medium-quality reviews are those with scores between four and seven, and low-quality reviews are those with scores less than four. It is important to note that the AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to systematic reviews pertaining to health-system arrangements or to economic and social responses to COVID-19. Where the denominator is not 11, an aspect of the tool was considered not relevant by the raters. In comparing ratings, it is therefore important to keep both parts of the score (i.e., the numerator and denominator) in mind. For example, a review that scores 8/8 is generally of comparable quality to a review scoring 11/11; both ratings are considered 'high scores.' A high score signals that readers of the review can have a high level of confidence in its findings. A low score, on the other hand, does not mean that the review should be discarded, merely that less confidence can be placed in its findings and that the review needs to be examined closely to identify its limitations. (Lewin S, Oxman AD, Lavis JN, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP): 8. Deciding how much confidence to place in a systematic review. *Health Research Policy and Systems* 2009; 7 (Suppl1):S8.

Preparing the profile

Each included document is hyperlinked to its original source to facilitate easy retrieval. For all included guidelines, systematic reviews, rapid reviews and single studies (when included), we prepare a small number of bullet points that provide a brief summary of the key findings, which are used to summarize key messages in the text. Protocols and titles/questions have their titles hyperlinked given that findings are not yet available. For this profile, we only prepared bulleted summaries of key findings for documents deemed to be of high relevance. For those classified as medium or low relevance, we list the title with a link to the primary source for easy retrieval if needed. We then draft a brief summary that highlights the total number of different types of highly relevant documents identified (organized by document), as well as their key findings, date of last search (or date last updated or published), and methodological quality.

Appendix 2: Key findings from evidence documents that address the question, organized by document type and sorted by relevance to the question and monkeypox

Type of document	Relevance to question	Key findings	Recency or status
Guidelines			
Full systematic reviews	<ul style="list-style-type: none"> Epidemiology (including transmission) 	<ul style="list-style-type: none"> This systematic review examined peer-reviewed and grey literature on the transmission of monkeypox, including the number of confirmed, probable, and/or possible cases, geographic spread, and patient characteristics Research on monkeypox documented a total of 48 confirmed and probable cases reported in six African countries during the 1970s, which increased over the next several decades but was not reported outside Africa until 2003 in the United States From 2009-19 there have been almost 20,000 suspected or confirmed cases of monkeypox, and of those cases one case was in Israel in 2018, three in the U.K. in 2018 and one in 2019, and one in Singapore in 2019 The median age at presentation has increased from four to five years old from 1970-1989 to 21 years in 2010-19, with cases outside of Africa even higher and occurring most frequently in adult males The authors hypothesize that this increase may be due to the cessation of smallpox vaccinations, which provided some cross-protection against monkeypox <p>Source (4/11 AMSTAR rating)</p>	Literature last searched 7 September 2020
	<ul style="list-style-type: none"> Epidemiology (including transmission) 	<ul style="list-style-type: none"> Monkeypox is characterized by a pustular rash indistinguishable from smallpox, and outcomes can range from severe to fatal Remote populations in Central and West Africa are most affected by outbreaks with the recent outbreaks occurring for the first time in 20 years in Nigeria and Cameroon There is an increase in reported outbreaks and number of cases by year in the Democratic Republic of Congo (DRC) and number of outbreak reports per year in the Central African Republic, but data are insufficient to measure trends in secondary attack rates and case-fatality rates 	Literature last searched 15 August 2018

Type of document	Relevance to question	Key findings	Recency or status
		<ul style="list-style-type: none"> Outside of DRC, there has been a notable increase in number of individual monkeypox outbreak reports between 2010 and 2018, particularly in the Central African Republic, but it is noted that this does not necessarily translate to an increase in annual cases over time in these areas In Nigeria, geographical patterns of infections suggest a possible new and widespread zoonotic reservoir Limited and anecdotal evidence exists for the use of antibiotics for prophylaxis against secondary cutaneous infection <p>Source (AMSTAR rating 6/11)</p>	
Rapid reviews	No rapid reviews identified		
Non-systematic reviews	<ul style="list-style-type: none"> Biology Epidemiology (including transmission) Prevention and control Clinical presentation Diagnosis Treatment 	<ul style="list-style-type: none"> Monkeypox is a zoonotic disease caused by the monkeypox virus (MPXV) which is a member of the orthopoxvirus genus The two possible means of MPXV transmission are animals-to-human transmission and human-to-human transmission, and respiratory droplets and contact with body fluids, contaminated patient's environment or items, skin lesion of an infected person associated with inter-human transmission <ul style="list-style-type: none"> Animal-to-human transmission occurs through direct contact with the above viral hosts or by direct contact with blood Human-to-animal transmission has not been reported Monkeypox symptoms present in three phases including an incubation period of four to 21 days, followed by a prodromal illness with signs including lymph node enlargement, headache, fever, back pain, myalgia, intense asthenia, pharyngitis, sweating and malaise, followed by an exanthema phase that includes vesiculopustular rashes that appear within one to 10 days spread over the body Vaccination against smallpox provides cross-protection against other OPV species including MPXV (monkeypox) 	Published 12 November 2020

Type of document	Relevance to question	Key findings	Recency or status
		<p>and many patients were born after the cessation of smallpox eradication program</p> <ul style="list-style-type: none"> • Diagnosis of monkeypox can occur through genetic methods (i.e., PCR or RT-PCR), phenotypic methods based on clinical diagnosis, immunological methods including IgG and IgM antibody detection and immunohistochemistry for viral antigen detection, and electron microscopy • Antivirals such as Tecovirimat, Cidofovir and Brincidofovir have shown efficacy in in vitro and animal studies, but their effectiveness in humans is unknown <ul style="list-style-type: none"> ○ Brincidofovir may have an improved safety profile compared to Cidofovir ○ Cidofovir and Brincidofovir may be considered in severe cases of monkeypox ○ Human clinical trials of Tecovirimat suggested that the drug was safe and tolerable with only minor side effects <p>Source</p>	
	<ul style="list-style-type: none"> • Epidemiology (including transmission) • Prevention and control • Clinical presentation • Diagnosis • Prognosis • Treatment 	<ul style="list-style-type: none"> • The frequency and geographic distribution of human monkeypox cases across West and Central Africa have increased in recent years <ul style="list-style-type: none"> ○ Monkeypox is largely found in rodents and has been detected in squirrels, rats, mice, and monkeys ○ Indirect or direct contact with live or dead animals is assumed to be the main source of human monkeypox infections ○ Secondary human-to-human transmission is considered common and presumably occurs through respiratory droplets or indirect or direct contact with body fluids, lesion material and contaminated surfaces or other material • The clinical presentation of monkeypox is similar to smallpox but generally less severe <ul style="list-style-type: none"> ○ Incubation period is estimated at five to 21 days, and symptoms and signs at two to five weeks 	Published December 2019

Type of document	Relevance to question	Key findings	Recency or status
		<ul style="list-style-type: none"> ○ The illness begins with non-specific symptoms and signs including fever, chills, headaches, lethargy, asthenia, lymph node swelling, back pain, and myalgia, followed by rashes of varying size that appear first on the face then across the body, hands, legs, and feet ○ Complications can include secondary bacterial infections, respiratory distress, broncho-pneumonia, encephalitis, corneal infection with vision loss, gastrointestinal involvement, vomiting, and diarrhea with dehydration ○ Case fatality rates have varied from 1% to 10% and occur mostly among young adults and children, especially those with immunosuppression ● Most confirmed monkeypox cases are younger than 40 years old, a population born after the discontinuation of the smallpox vaccination campaign, possibly reflecting a lack of cross-protective immunity <ul style="list-style-type: none"> ○ Prevention measures for animal-to-human transmission include avoiding contact with rodents and primates, limiting direct exposure to blood and inadequately cooked meat, and using personal protective equipment when handling potential animal reservoir species ○ Prevention measures for human-to-human transmission include avoiding close contact with anyone infected and healthcare providers using personal protective equipment when treating infected patients ● For diagnosis, optimal clinical specimens for laboratory analyses include those from skin lesions, exudate, or crusts stored in a dry, sterile tube (without viral transport media) and kept cold <ul style="list-style-type: none"> ○ Analysis should be carried out using electron microscopy through polymerase chain reaction ● Monkeypox is treated through supportive care, symptomatic management, and treatment of secondary bacterial infections 	

Type of document	Relevance to question	Key findings	Recency or status
	<ul style="list-style-type: none"> • Biology • Epidemiology (including transmission) • Prevention and control • Clinical presentation • Diagnosis • Prognosis • Treatment 	Source <ul style="list-style-type: none"> • This review looked at the monkeypox infection in Nigeria, its most recent biology, virus-host interaction, epidemiology, diagnosis, chemotherapy, prevention, and control strategies • The monkeypox virus falls into two distinct strains, based on genetic, geographic, and phenotypic variation, these being the West African and the Congo Basin groups, with defined epidemiological and clinical differences • Transmission to humans is primarily by exposure to animal reservoirs (primary zoonotic transmission), such as squirrels • The most recent outbreak in Nigeria started in September 2017 and currently, this is the largest outbreak caused by the West African strain, and further investigation measures are in place to improve the existing knowledge to ensure effective prevention and control strategies • The clinical presentation of the monkeypox virus largely resembles that of smallpox, with an incubation period of seven to 17 days, and includes fever, muscle aches, backache, lymphadenopathy, followed by lesions and rashes all over the body • The recent development and license of Tecovirimat as an antipoxvirus cure is an achievement in antiviral therapy • Public health measures, such as case isolation, contact tracing, avoiding contact with animals or materials suspected of being infected, use of personal protective equipment and good hand-hygiene practices, remain the best measures for preventing and controlling human monkeypox 	Published April 2019
	<ul style="list-style-type: none"> • Biology • Epidemiology (including transmission) • Clinical presentation 	Source <ul style="list-style-type: none"> • This review looked at the history and evolution of monkeypox outbreaks in Africa and the United Kingdom, the changing clinical presentations, and the possible factors underlying the increasing numbers being detected 	Published January 2019

Type of document	Relevance to question	Key findings	Recency or status
		<ul style="list-style-type: none"> Clinical presentations of the monkeypox virus include symptoms with skin and mucosal lesions which are difficult to distinguish from smallpox, and the infection starts with fever, headache, back pain, myalgia and asthenia followed by eruption of skin and mucosal lesions starting with the face The exact mode of transmission of the monkeypox virus to humans remains unknown <ul style="list-style-type: none"> It is assumed that animal-to-human infection occurs through direct or indirect contact with monkeypox-infected animal bodily fluids through handling, bites or scratches Current evidence suggests that the outbreak is caused by multiple source emergence into the human population, and not sustained by human-to-human transmission Most of the currently available data on monkeypox comes from individual cases or outbreak reports which do not provide an overall accurate picture There are current knowledge gaps in the epidemiology, host reservoir, emergence, transmission, pathogenesis, and prevention of monkeypox The authors noted that there is a need to build public health and surveillance capacities across Africa Source	
	<ul style="list-style-type: none"> Prevention and Control 	<ul style="list-style-type: none"> In many parts of Africa, frontline healthcare workers are at risk of contracting and transmitting monkeypox, and so vulnerable clinical settings must work to strengthen infection prevention and control protocols including the use of personal protective equipment The smallpox vaccine can offer a secondary prevention strategy to prevent infection of monkeypox in healthcare workers Source	Published February 2019
	<ul style="list-style-type: none"> Biology Clinical presentation Diagnosis 	<ul style="list-style-type: none"> Human monkeypox - After 40 years, an unintended consequence of smallpox eradication Source	Published 14 July 2020

Type of document	Relevance to question	Key findings	Recency or status
	<ul style="list-style-type: none"> Treatment 		
Protocols for reviews that are already underway			
Titles and questions for reviews being planned			
Single studies	<ul style="list-style-type: none"> Epidemiology (including transmission) Prevention and Control Clinical Presentation 	<ul style="list-style-type: none"> The study describes an imported case of monkeypox from Nigeria to the United Kingdom, whereby secondary transmissions occurred within the family to an adult and toddler After arriving to the U.K., Case 1 developed a vesicular lesion <ul style="list-style-type: none"> By day 19, Case 1 was afebrile, lesions had crusted, and they tested negative for monkeypox by PCR in urine, blood, lesion fluid, and nose/throat swab 19 days after Case 1 symptoms' onset, their 18-month-old child developed lesions 33 days after Case 1 symptoms' onset, an adult member of the family developed a vesicular rash, and had confirmed monkeypox Contacts of Case 1 included household contacts, healthcare workers, hospital laundry workers, and members of the public <ul style="list-style-type: none"> 30 contacts in Wales were identified for active surveillance as they had direct exposure of broken skin or mucous membranes to a symptomatic patient, and they were contacted daily for 21 days by Public Health Wales to check for symptoms; eight were identified for passive surveillance <p>Source</p>	Published 21 August 2021
	<ul style="list-style-type: none"> Epidemiology (including transmission) Clinical presentation Diagnosis 	<ul style="list-style-type: none"> A suspected monkeypox case was defined as an individual with a vesicular or pustular rash with deep-seated, firm pustules, and ≥ 1 of the following symptoms: fever preceding the eruption, lymphadenopathy (inguinal, axillary, or cervical), or pustules or crusts on the palms of the hands or soles of the feet 	Published 4 June 2021

Type of document	Relevance to question	Key findings	Recency or status
		<ul style="list-style-type: none"> • A confirmed monkeypox case requires detection of Orthopoxvirus or MPXV DNA with real-time polymerase chain reaction (PCR) or isolation of MPXV in culture from ≥ 1 specimen • Swab eluates, crust homogenates, or blood from suspected cases were used to test monkeypox infection • Based on data obtained from monkeypox surveillance from 2011–15 in Tshuapa Province, DRC, the study evaluated differences in cumulative incidence, exposure histories, and clinical presentation of laboratory-confirmed monkeypox cases by sex and age groups • The following findings were reported for the period 2011–15: <ul style="list-style-type: none"> ○ The average annual incidence was 14.1 per 100,000 ○ The incidence was higher in male patients except among those 20–29 years old, but females aged 20–29 years also reported a high frequency of exposure (26.2%) to people with monkeypox-like symptoms ○ The highest incidence was among 10-to-19-year-old males, the cohort reporting the highest proportion of animal exposures (37.5%) ○ The incidence was lower among those presumed to have received smallpox vaccination than among those presumed unvaccinated ○ No differences were observed by age group in lesion count or lesion severity score ○ Monkeypox incidence was twice that reported during 1980–85 • In conclusion, the increase in the incidence of monkeypox might be linked to declining immunity provided by smallpox vaccination • The high proportion of cases attributed to human exposures suggests changing exposure patterns <p>Source</p>	
	<ul style="list-style-type: none"> • Clinical presentation • Prognosis 	<ul style="list-style-type: none"> • This study describes the clinical course and management of 40 hospitalized monkeypox cases during the 2017–18 	Published 15 October 2020

Type of document	Relevance to question	Key findings	Recency or status
		<p>human monkeypox outbreak in Nigeria using retrospective records</p> <ul style="list-style-type: none"> • The most common clinical features observed (in order) included skin rash, fever, lymphadenopathy, genital ulcers, body aches, headache, sore throat, pruritus, and conjunctivitis and photophobia • The most common first symptoms were rash and fever • Twenty-one (52.5%) of 40 cases developed one or more complications including (in order of frequency) secondary bacterial infection, gastroenteritis, sepsis, bronchopneumonia, encephalitis, keratitis, and premature rupture of membrane at 16 weeks' gestation and resultant intrauterine fetal death • Patients with HIV type 1 co-infection were significantly more likely to have larger skin rashes, genital ulcers, secondary bacterial infection, and longer duration of illness • Five (12.5%) of the 40 cases died • Sequelae observed amongst 18 patients discharged from hospital and seen at follow-up included hyperpigmented atrophic scars, patchy alopecia, hypertrophic skin scarring, and contracture/deformity of facial muscles; three of the 18 patients showed complete healing after eight weeks of follow-up <p>Source</p>	
	<ul style="list-style-type: none"> • Epidemiology (including transmission) 	<ul style="list-style-type: none"> • This study uses historical data from the Democratic Republic of the Congo to estimate the reproduction number (R) and basic reproduction number (R0) of smallpox and monkeypox in a population with imperfect immunity • In the early 1980s, when smallpox vaccination had nearly 100% coverage in the country and the vaccination campaign ended, it was estimated monkeypox had an R value of 0.32 (uncertainty interval (UI): 0.22-0.40) and an R0 value of 2.13 (UI: 1.46-2.67) 	Published 8 July 2020

Type of document	Relevance to question	Key findings	Recency or status
		<ul style="list-style-type: none"> • With data from 2011-12 that indicate a 60% population immunity against orthopoxvirus species, the R value for monkeypox was calculated to be 0.85 (UI: 0.51-1.25) • The authors propose two theories for how monkeypox could become endemic in the Democratic Republic of the Congo: <ul style="list-style-type: none"> ○ Frequent outbreaks with $R < 1$ may occur due to involuntary human contact with animal reservoirs ○ Monkeypox may undergo sustained human-to-human transmission ($R > 1$) ○ In either case, the authors note that repeated circulation in humans favours pathogen evolution and the emergence of human-adapted pathogens • The authors note that their estimates rely on data for the Democratic Republic of the Congo and may differ for areas with virus clades, societal structures, population densities, and residual orthopoxvirus immunity <p>Source</p>	
	<ul style="list-style-type: none"> • Epidemiology (including transmission) 	<ul style="list-style-type: none"> • This study described the transmission of monkeypox virus from an investigation that Public Health England (PHE) conducted of two unrelated cases of monkeypox that affected travellers returning from Nigeria • A clinical diagnosis of suspected monkeypox was made for the second of these patient cases, and infection prevention and control measures for an infectious disease were implemented, including enhanced personal protective equipment (PPE) consisting of disposable gown, disposable gloves, filtering facepiece of the respirator, and face shield or goggles • The patient was transferred to an airborne infectious disease treatment centre, and monkeypox was confirmed by PHE • Transmission may occur through close contact with skin lesions of an infected person, via fomites, or by exposure to large respiratory droplets during face- to-face contact 	Published April 2020

Type of document	Relevance to question	Key findings	Recency or status
		<ul style="list-style-type: none"> • Transmission of monkeypox occurred between the second patient to a healthcare worker, and most likely the only exposure risk identified during assessment of the infected healthcare worker was the changing of potentially contaminated bedding, when patient 2 had multiple skin lesions but before a diagnosis of monkeypox had been considered • It was deemed that the risk to the public is very low as the effective human to human transmission requires close contact with an infected individual or virus-contaminated materials, however, monkeypox is considered a high-consequence infectious disease in England Source	
	<ul style="list-style-type: none"> • Clinical presentation • Prognosis 	<ul style="list-style-type: none"> • This study uses a cross-sectional sample of 223 confirmed cases from a monkeypox surveillance program in the Democratic Republic of the Congo to investigate the association between exposure to rodents and non-human primates with rash severity amongst confirmed cases • Rash severity was classified as either mild (5-100 lesions) or severe (>100 lesions) • Those with confirmed monkeypox tended to be younger, male, and live in forested areas • Hunting of non-human primates was associated with rash severity in both unadjusted and adjusted models (OR= 2.78 (95% CI: 1.18, 6.58)), while exposure to non-human primates was associated with rash severity only in an unadjusted model • There was no association found between rodent exposure and monkeypox rash severity Source	Published 24 December 2019
	<ul style="list-style-type: none"> • Epidemiology (including transmission) • Clinical presentation 	<ul style="list-style-type: none"> • This cross-sectional study was conducted in Mfou district, Cameroon one year after a monkeypox outbreak involving captive chimpanzees • The goals of the study were to describe the seroprevalence of orthopoxviruses and explore factors associated with 	Published 25 November 2019

Type of document	Relevance to question	Key findings	Recency or status
		<p>exposure to bushmeat amongst employees of a primate sanctuary and residents of nearby villages</p> <ul style="list-style-type: none"> • A total of 125 participants were recruited • Forty-three participants (34.4%) were IgG positive for anti-orthopoxvirus antibodies; however, amongst those born after the era of routine smallpox vaccination only four (6.3%) were positive for anti-orthopoxvirus antibodies • These four individuals did not report histories of smallpox-like disease or have contact with sick chimpanzees during the outbreak • The presence of anti-orthopoxvirus antibodies in individuals born after the era of smallpox vaccination suggests the possibility of asymptomatic circulation of an orthopoxvirus (which was most likely monkeypox) in human populations <p>Source</p>	
	<ul style="list-style-type: none"> • Epidemiology (including transmission) • Clinical presentation 	<ul style="list-style-type: none"> • This study aimed to describe the clinical and epidemiological features of the 2017 to 2018 human monkeypox outbreak in Nigeria, the largest documented human outbreak of the west African strain of the monkeypox virus • Data was collected with a standardized case investigation form based on a case definition of human monkeypox from previously established guidelines • Diagnosis of the human monkeypox virus infection was confirmed by viral identification with real-time PCR and detection of antibodies • The results showed that 122 confirmed or probable cases of human monkeypox were recorded in 17 states of Nigeria, infecting individuals from the ages of two to 50 years • All patients had rashes on all parts of the body, fever, headaches, and lymphadenopathy 	Published August 2019

Type of document	Relevance to question	Key findings	Recency or status
		<ul style="list-style-type: none"> The results suggest endemicity of monkeypox virus in Nigeria, with some evidence of human-to-human transmission Source	
	<ul style="list-style-type: none"> Epidemiology (including transmission) Prevention and control 	<ul style="list-style-type: none"> A cross-sectional study was conducted between 25 September and 31 December 2017 to review clinical and laboratory characteristics of all suspected and confirmed cases of human monkeypox identified at Niger Delta University Teaching Hospital, and to appraise its plans, activities and challenges in responding to the outbreak To respond to the outbreak, the hospital established a make-shift isolation ward for case management by a monkeypox response team and provided infection and control resources Challenges identified included: some healthcare workers being reluctant to participate in the outbreak with some avoiding suspected patients; stigma and discrimination experienced by patients and their family members; and refusal of isolation Continued training was offered, and using a collaborative approach among all involved stakeholders addressed some of these challenges and eventually led to successful containment of the outbreak Source	Published 17 April 2019
	<ul style="list-style-type: none"> Biology Epidemiology (including transmission) 	<ul style="list-style-type: none"> The study consisted of an outbreak investigation involving human monkeypox cases from four districts (Impfondo, Betou, Dongou, and Enyelle) in the Likouala department of the Republic of the Congo Active and retrospective cases were identified and reported by health facilities, patients, and family and community members Confirmed and suspected monkeypox cases were investigated and data was collected using the Ministry of Health's standardized case report form The authors of the study investigated 43 suspected human monkeypox cases during the period of 22 March and 5 	Published February 2019

Type of document	Relevance to question	Key findings	Recency or status
		<p>April in 2017 by interviewing suspected case patients and collecting dried blood strips and vesicular and crust specimens from active lesions, and narrowed the number down to 22 confirmed, probable, and possible cases</p> <ul style="list-style-type: none"> • The results showed that there were no epidemiologic links between cases from different districts, and all hypothesized human to human transmission events appeared to have been contained within the individual districts • There was no evidence suggesting that the virus was introduced from neighbouring countries • The authors noted some challenges associated with the remote regions of the districts, such as limited health and transportation infrastructure, absence of specimen collection supplies, and a well-functioning cold chain, that would have resulted in inconsistent and incomplete reporting <p>Source</p>	
	<ul style="list-style-type: none"> • Epidemiology (including transmission) • Prevention and control 	<ul style="list-style-type: none"> • Three different thresholds to trigger a public-health response to monkeypox were evaluated using surveillance data from Tshuapa Province in the Democratic Republic of Congo from 2011-13 • Three different statistical thresholds were used: Cullen, c-sum, and a World Health Organization (WHO) method based on monthly incidence • The study concluded that using signals detected by a single method may be inefficient and overly simplistic for triggering public-action for monkeypox • Instead, a response algorithm is proposed which integrates the WHO method as an objective threshold with contextual information about epidemiological and spatiotemporal links between suspected cases • This approach can be used to determine whether routine surveillance, alert status, or outbreak status are needed and can be modified for use in different countries <p>Source</p>	Published 20 December 2018

Type of document	Relevance to question	Key findings	Recency or status
	<ul style="list-style-type: none"> Treatment 	<ul style="list-style-type: none"> While smallpox was eradicated in 1980, the variola virus (VARV) causing smallpox, still exists <ul style="list-style-type: none"> Tecovirimat is currently developed as an oral smallpox therapy This study evaluated the efficacy of tecovirimat in non-human primate (monkeypox) and rabbit (rabbitpox) models, along with a safety trial involving 449 human adults The minimum dose of Tecovirimat required to achieve >90% survival in the monkeypox model was 10 mg per kilogram of body weight for 14 days, and 40 mg per kilogram in the rabbitpox model The monkeypox model was more effective in estimating required drug exposure in humans A dose of 600 mg twice daily for 14 days was used to test in humans, and no troubling adverse events were observed <p>Source</p>	Published 5 July 2018
	<ul style="list-style-type: none"> Epidemiology (including transmission) Prevention and Control 	<ul style="list-style-type: none"> The majority of monkeypox cases occurred in the Democratic Republic of the Congo (DRC); however, in the last decade, the number of cases in other African countries have been increasing Nigeria is currently experiencing the largest outbreak of human monkeypox with 80 confirmed cases The closer contact between animals and humans through deforestation, climate change, hunting, and population movement might be a factor in the increasing recent cases Robust disease surveillance systems with initial and long-term financial and human resource investment are required to stop the further spread of monkeypox <ul style="list-style-type: none"> Currently, no mandatory reporting is required through the Integrated Disease Surveillance and Response system across Africa, but it is recommended Coordination of interventions and routine sharing of information between human and wildlife sectors is necessary because monkeypox is a zoonotic disease <p>Source</p>	Published 16 March 2018

Type of document	Relevance to question	Key findings	Recency or status
	<ul style="list-style-type: none"> • Diagnosis • Prevention and Control • Prognosis • Treatment 	<ul style="list-style-type: none"> • This observational study reported on fetal outcomes for one of four pregnant women who participated in an observational study at the General Hospital of Kole (Sankuru Province in the Democratic Republic of Congo), where 222 symptomatic subjects were followed from 2007 to 2011 • Diagnosis: <ul style="list-style-type: none"> ○ Patients meeting the WHO case definition of MPXV infection, which uses clinical findings and history, were enrolled in the study ○ Laboratory confirmation of infection was conducted by polymerase chain reaction (PCR) analysis of blood specimens or samples of other bodily fluids ○ Staff used the WHO clinical severity score based on the number of skin lesions to classify cases of human monkeypox • Prevention, control and Treatment: <ul style="list-style-type: none"> ○ During hospitalization, pregnant women received antibiotics (amoxicillin, chloramphenicol via eye drops, and erythromycin, as well as gentamycin, if necessary) for prevention or control of bacterial superinfection, paracetamol and papaverine were given as analgesics, metronidazole and mebendazole were administered for giardiasis and other intestinal parasitic infections, and quinine as given for malaria • Prognosis: <ul style="list-style-type: none"> ○ Three of 4 pregnant women identified as having MPXV infection experienced fetal demise • Findings of this study confirm that maternal MPXV infection may have adverse consequences for the fetus without apparent correlation with severity of maternal disease • Further studies should focus on the relatively high risk of fetal demise among pregnant women with MPXV <p>Source</p>	Published 17 October 2017

Type of document	Relevance to question	Key findings	Recency or status
	<ul style="list-style-type: none"> Clinical presentation Diagnosis 	<ul style="list-style-type: none"> This study used cohort data from 2009 to 2014 from Democratic Republic of Congo to evaluate two surveillance case definitions for monkeypox and clinical characteristics associated with confirmed cases The cohort included 333 laboratory confirmed cases of monkeypox, 383 laboratory confirmed varicella zoster virus cases, and 36 cases that were confirmed not to be either of these viruses It was found that monkeypox and varicella zoster viruses presented with several of the same signs and symptoms, including key rash characteristics, and identified 12 specific signs/symptoms that are important to look for when investigating monkeypox cases The analysis used 12 signs and symptoms that were identified as having high sensitivity and/or specificity values, and found that monkeypox cases with fever before a rash in addition to seven or eight of the other signs and symptoms had a more balanced performance between sensitivity and specificity However, a surveillance case definition with more specificity was identified as being needed to be able to document and detect endemic human monkeypox cases, and that laboratory-confirmed diagnosis is needed in the absence of such a definition <p>Source</p>	Published 11 September 2017
	<ul style="list-style-type: none"> Biology Clinical presentation Diagnosis 	<ul style="list-style-type: none"> This study used in vivo bioluminescent imaging (BI) to study monkeypox virus infection from Central Africa in laboratory and wild-caught animals by experimentally infecting African wild-caught rope squirrels via intranasal and intradermal exposure After infection, the study researchers monitored viral replication and shedding of the monkeypox virus via in vivo BI, viral cultures, and real-time PCR The results showed that monkeypox virus infection in African rope squirrels caused mortality and moderate to 	Published 21 August 2017

Type of document	Relevance to question	Key findings	Recency or status
		<p>severe morbidity, with clinical signs including pox lesions in the skin, eyes, mouth and nose</p> <ul style="list-style-type: none"> Intranasal and intradermal exposures induced high levels of viremia, fast systemic spread, and long periods of viral shedding, in which viral shedding was still detectable after 15 days post-infection The study shows that rope squirrels shed large quantities of the virus and for long periods, supporting the hypothesis that they play a potential role in monkeypox virus transmission to humans and other animals in the Central African region <p>Source</p>	
	<ul style="list-style-type: none"> Epidemiology (including transmission) Prevention and control Treatment 	<ul style="list-style-type: none"> Imported monkeypox from international traveller, Maryland, U.S., 2021 <p>Source</p>	Published May 2022
	<ul style="list-style-type: none"> Epidemiology (including transmission) 	<ul style="list-style-type: none"> Exportation of monkeypox virus from the African continent <p>Source</p>	Published 19 April 2022
	<ul style="list-style-type: none"> Biology Epidemiology (including transmission) Prevention and control 	<ul style="list-style-type: none"> Monkeypox in a traveller returning from Nigeria - Dallas, Texas, July 2021 <p>Source</p>	Published 8 April 2022
	<ul style="list-style-type: none"> Treatment 	<ul style="list-style-type: none"> New methylene blue derivatives suggest novel anti-orthopoxviral strategies <p>Source</p>	Published July 2021
	<ul style="list-style-type: none"> Biology 	<ul style="list-style-type: none"> Genomic history of human monkey pox infections in the Central African Republic from 2001 to 2018 <p>Source</p>	Published 22 June 2021
	<ul style="list-style-type: none"> Epidemiology (including transmission) 	<ul style="list-style-type: none"> Re-emergence of human monkeypox and declining population immunity in the context of urbanization, Nigeria, 2017-20 <p>Source</p>	Published April 2021
	<ul style="list-style-type: none"> Epidemiology (including transmission) Clinical presentation Diagnosis Prognosis 	<ul style="list-style-type: none"> Human monkeypox virus infection in plateau state, north central Nigeria: a report of two cases <p>Source</p>	Published 30 December 2021

Type of document	Relevance to question	Key findings	Recency or status
	<ul style="list-style-type: none"> Treatment 		
	<ul style="list-style-type: none"> Diagnosis 	<ul style="list-style-type: none"> CRISPR/Cas9 as an antiviral against orthopoxviruses using an AAV vector Source 	Published 9 November 2020
	<ul style="list-style-type: none"> Prevention and control 	<ul style="list-style-type: none"> Imported monkeypox, Singapore Source 	Published August 2020
	<ul style="list-style-type: none"> Prevention and control 	<ul style="list-style-type: none"> Assessment of media reportage of monkeypox in southern Nigeria Source 	Published January 2020
	<ul style="list-style-type: none"> Biology Epidemiology (including transmission) Clinical presentation 	<ul style="list-style-type: none"> Monkeypox virus emergence in wild chimpanzees reveals distinct clinical outcomes and viral diversity Source 	Published July 2020
	<ul style="list-style-type: none"> Biology 	<ul style="list-style-type: none"> Comparison of multiplexed immunofluorescence imaging to chromogenic immunohistochemistry of skin biomarkers in response to monkeypox virus infection 	Published 23 July 2020
	<ul style="list-style-type: none"> Prevention and control 	<ul style="list-style-type: none"> Confidence in managing human monkeypox cases in Asia: A cross-sectional survey among general practitioners in Indonesia Source 	Published June 2020
	<ul style="list-style-type: none"> Prevention and control 	<ul style="list-style-type: none"> Knowledge of human monkeypox viral infection among general practitioners: a cross-sectional study in Indonesia Source 	Published March 2020
	<ul style="list-style-type: none"> Prevention and control 	<ul style="list-style-type: none"> Use of surveillance outbreak response management and analysis system for human monkeypox outbreak, Nigeria, 2017-19 Source 	Published February 2020
	<ul style="list-style-type: none"> Prevention and control 	<ul style="list-style-type: none"> Co-administration of Tecovirimat and ACAM2000™ in non-human primates: Effect of Tecovirimat treatment on ACAM2000 immunogenicity and efficacy versus lethal monkeypox virus challenge Source 	Published 16 January 2020
	<ul style="list-style-type: none"> Epidemiology (including transmission) 	<ul style="list-style-type: none"> Do monkeypox exposures vary by ethnicity? Comparison of Aka and Bantu suspected monkeypox cases Source 	Published January 2020

Type of document	Relevance to question	Key findings	Recency or status
	<ul style="list-style-type: none"> Epidemiology (including transmission) 	<ul style="list-style-type: none"> Temporal and spatial dynamics of monkeypox in democratic republic of Congo, 2000-2015 Source 	Published September 2019
	<ul style="list-style-type: none"> Epidemiology (including transmission) Clinical presentation Diagnosis 	<ul style="list-style-type: none"> Human monkeypox in Sierra Leone after 44-year absence of reported cases Source 	Published May 2019
	<ul style="list-style-type: none"> Epidemiology (including transmission) Treatment 	<ul style="list-style-type: none"> Intrafamily transmission of monkeypox virus, Central African Republic, 2018 Source 	Published August 2019
	<ul style="list-style-type: none"> Diagnosis 	<ul style="list-style-type: none"> Recombinase polymerase amplification assay for rapid detection of Monkeypox virus Source 	Published September 2019
	<ul style="list-style-type: none"> Biology Diagnosis 	<ul style="list-style-type: none"> Molecular evidence of human monkeypox virus infection, Sierra Leone Source 	Published June 2019
	<ul style="list-style-type: none"> Biology Epidemiology (including transmission) Clinical presentation 	<ul style="list-style-type: none"> Diagnosis of imported monkeypox, Israel, 2018 Source 	Published May 2019
	<ul style="list-style-type: none"> Diagnosis 	<ul style="list-style-type: none"> Preliminary screening and in vitro confirmation of orthopoxvirus antivirals Source 	Published 2019
	<ul style="list-style-type: none"> Epidemiology (including transmission) Prevention and control 	<ul style="list-style-type: none"> Two cases of monkeypox imported to the United Kingdom, September 2018 Source 	Published September 2018
	<ul style="list-style-type: none"> Epidemiology (including transmission) 	<ul style="list-style-type: none"> Investigation of an outbreak of monkeypox in an area occupied by armed groups, Central African Republic Source 	Published June 2018
	<ul style="list-style-type: none"> Diagnosis 	<ul style="list-style-type: none"> Intranasal monkeypox marmoset model: Prophylactic antibody treatment provides benefit against severe monkeypox virus disease Source 	Published 21 June 2018
	<ul style="list-style-type: none"> Biology 	<ul style="list-style-type: none"> Genomic characterization of human monkeypox virus in Nigeria Source 	Published March 2018

Type of document	Relevance to question	Key findings	Recency or status
	<ul style="list-style-type: none"> Clinical presentation 	<ul style="list-style-type: none"> Improving the care and treatment of monkeypox patients in low-resource settings: applying evidence from contemporary biomedical and smallpox biodefense research Source	Published 12 December 2017
	<ul style="list-style-type: none"> Diagnosis 	<ul style="list-style-type: none"> Validation of a pan-orthopox real-time PCR assay for the detection and quantification of viral genomes from non-human primate blood Source	Published 3 November 2017
	<ul style="list-style-type: none"> Biology Epidemiology (including transmission) 	<ul style="list-style-type: none"> Assessing monkeypox virus prevalence in small mammals at the human-animal interface in the Democratic Republic of the Congo Source	Published 3 October 2017
	<ul style="list-style-type: none"> Epidemiology (including transmission) 	<ul style="list-style-type: none"> Varicella co-infection in patients with active monkeypox in the Democratic Republic of the Congo Source	Published September 2017
	<ul style="list-style-type: none"> Prevention and control 	<ul style="list-style-type: none"> A single vaccination of non-human primates with highly attenuated smallpox vaccine, lc16m8, provides long-term protection against monkeypox Source	Published 24 July 2017
	<ul style="list-style-type: none"> Biology 	<ul style="list-style-type: none"> Monkeypox virus host factor screen using haploid cells identifies essential role of GARP complex in extracellular virus formation Source	Published 12 May 2017
	<ul style="list-style-type: none"> Epidemiology (including transmission) 	<ul style="list-style-type: none"> Presumptive risk factors for monkeypox in rural communities in the Democratic Republic of the Congo Source	Published 13 February 2017
	<ul style="list-style-type: none"> Treatment 	<ul style="list-style-type: none"> Pharmacokinetics and efficacy of a potential smallpox therapeutic, Brincidofovir, in a lethal monkeypox virus animal model Source	Published 3 February 2021
	<ul style="list-style-type: none"> Epidemiology (including transmission) Clinical presentation 	<ul style="list-style-type: none"> A tale of two viruses: co-infections of monkeypox and varicella zoster virus in the Democratic Republic of Congo Source	Published 7 December 2020

Type of document	Relevance to question	Key findings	Recency or status
	<ul style="list-style-type: none"> Prevention and control 	<ul style="list-style-type: none"> Acceptance and willingness to pay for a hypothetical vaccine against monkeypox viral infection among frontline physicians: A cross-sectional study in Indonesia Source 	Published 7 October 2020
	<ul style="list-style-type: none"> Biology 	<ul style="list-style-type: none"> Analgesia during monkeypox virus experimental challenge studies in prairie dogs (<i>Cynomys ludovicianus</i>) Source 	Published 1 July 2019
	<ul style="list-style-type: none"> Biology 	<ul style="list-style-type: none"> Characterization of monkeypox virus dissemination in the black-tailed prairie dog (<i>Cynomys ludovicianus</i>) through in vivo bioluminescent imaging Source 	Published 26 September 2019
	<ul style="list-style-type: none"> Biology 	<ul style="list-style-type: none"> Monkeypox virus phylogenetic similarities between a human case detected in Cameroon in 2018 and the 2017-18 outbreak in Nigeria Source 	Published April 2019
	<ul style="list-style-type: none"> Treatment 	<ul style="list-style-type: none"> Effects of treatment delay on efficacy of Tecovirimat following lethal aerosol monkeypox virus challenge in cynomolgus macaques Source 	Published 22 September 2022
	<ul style="list-style-type: none"> Diagnosis 	<ul style="list-style-type: none"> Evaluation of the GeneXpert for human monkeypox diagnosis Source 	Published 8 February 2017
	<ul style="list-style-type: none"> Treatment 	<ul style="list-style-type: none"> Using the ground squirrel (<i>marmota bobak</i>) as an animal model to assess monkeypox drug efficacy Source 	Published February 2017

Appendix 3: Documents excluded at the final stages of reviewing

Type of document	Hyperlinked title
Guidelines	None identified
Full systematic reviews	None identified
Rapid reviews	None identified
Non-systematic reviews	Monkeypox re-emergence in Africa: A call to expand the concept and practice of One Health Review of poxvirus: Emergence of monkeypox
Protocols for reviews that are already underway	A systematic review of the availability, quality and inclusivity of supportive care guidelines in the management of high consequence infectious disease Systematic review of community-based responses to epidemic and pandemic diseases The impacts of e-health on the management of infectious disease outbreaks in low- and middle-income countries: A mixed-methods systematic review Utilization of children's emergency care services during epidemics and pandemics: a systematic review
Titles and questions for reviews being planned	None identified
Single studies	A genome-wide haploid genetic screen identifies heparan sulfate-associated genes and the macropinocytosis modulator TMED10 as factors supporting vaccinia virus infection Emergence of monkeypox in West Africa and Central Africa, 1970–2017 Genome sequences of akhmeta virus, an early divergent old world orthopoxvirus Importance of epidemiological research of monkeypox: Is incidence increasing? Monitoring healthcare professionals after monkeypox exposure: Experience from the first case imported to Asia Re-emergence of human monkeypox in Nigeria, 2017 Strengthening of surveillance during monkeypox outbreak, Republic of the Congo, 2017 [18 F]-Fluorodeoxyglucose uptake in lymphoid tissue serves as a predictor of disease outcome in the non-human primate model of monkeypox virus infection Varicella in Tshuapa Province, Democratic Republic of Congo, 2009-2014
Other types of documents	A case of imported Monkeypox in Singapore (Correspondence from The Lancet) Emergence of human monkeypox in West Africa (Commentary from The Lancet) Importance of epidemiological research of monkeypox: Is incidence increasing? (Editorial from Expert Review of Anti-infective Therapy) Monkeypox contacts: A puzzling problem (Editorial from The Lancet) Monkeypox: What do we know about the outbreaks in Europe and North America? (News and views from BMJ) Monkeypox transmission among international travellers - serious monkey business? (Editorial from Journal of Travel Medicine) Rinderpest, smallpox, and the imperative of destruction (Editorial from The Lancet) Seven monkeypox cases are confirmed in England (News and views from BMJ) Should we be already worried about monkeypox? (Editorial from Medicina Clínica) The evolving epidemiology of human monkeypox: Questions still to be answered (Editorial from Journal of Infectious Diseases) Toward understanding the outcomes of monkeypox infection in human pregnancy (Commentary from Journal of Infectious Diseases) Wildlife surveillance for emergent disease (News and views from Nature)