

SYNTHESIS

Multi-Jurisdictional Monkeypox Outbreak 2022 – What We Know So Far

2nd Revision: October 2022

Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to the worldwide monkeypox outbreak in 2022. “What We Know So Far” documents provide a rapid review of the evidence related to a specific aspect or emerging issue related to the 2022 worldwide monkeypox outbreak.

Key Findings

- Monkeypox is a viral zoonosis with a typical incubation period of 6 to 13 days (range = 5 to 21 days). Person-to-person transmission of monkeypox occurs via close contact with lesions, body fluids, respiratory secretions and materials contaminated with monkeypox virus.¹
- Sporadic monkeypox cases and outbreaks outside of endemic areas have been reported prior to 2022.
 - Genomic sequencing of a dozen cases from Germany, Portugal and Belgium suggests a single origin associated with the exportation of monkeypox virus from Nigeria to non-endemic countries (the UK, Israel and Singapore) in 2018 and 2019.
- In May 2022, over 400 confirmed monkeypox cases with no direct travel links to monkeypox endemic areas were reported from over 20 countries, including Europe, the United Kingdom, Canada and the United States. As of June 15, 2,013 lab-confirmed cases of monkeypox have been reported to the World Health Organization (WHO) from 42 countries since January 1, 2022.
- The epidemiological and clinical features of the 2022 outbreak in some European countries suggest human-to-human transmission via close contact, including close contact via sexual/intimate contact. Reported cases have mainly but not exclusively self-identified as men who have sex with men (MSM). Potential factors contributing to this multi-jurisdictional global surge in cases that have been proposed, or are being investigated, include:
 - Host/environment factors, e.g.:
 - Attendance at large-scale international events may have facilitated seeding of the monkeypox virus worldwide.
 - Lack of awareness of monkeypox among health care providers outside of endemic regions may have contributed to under-detection and subsequent low-level circulation of monkeypox.

- Lack of cross-protection from smallpox vaccination in younger populations as a result of the discontinuation of population-level immunization programs following global eradication of smallpox.¹
- Agent factors, e.g.:
 - Potential for mutations leading to increased transmissibility: 50 single nucleotide polymorphisms in the 2022 outbreak associated strain of the virus have been detected, compared to the monkeypox virus isolated in 2018 and 2019.
- Available evidence suggests that those who are most at risk are those who have had close physical contact with someone with monkeypox while they are symptomatic. The role of sexual bodily fluids (e.g., semen and vaginal fluids) in monkeypox transmission is currently unclear; however, several jurisdictions have recommended the use of contraceptive barriers for up to 12 weeks following resolution of infection as a precautionary measure.²
- Collaboration between human and veterinary public health is needed in view of the potential risk of human-to-animal transmission. The emerging epidemiology, and evidence concerning at risk populations, routes of transmission, and disease severity need to be carefully monitored to inform the public health response in Ontario.

Background

- Monkeypox is a zoonotic infection with symptoms similar to but less severe than those seen in smallpox patients.¹ It is caused by monkeypox virus, an enveloped virus within the *Orthopoxvirus* genus in the *Poxviridae* family,² first discovered in 1958 when outbreaks of a pox-like disease occurred in monkeys kept for research in a Danish laboratory.¹
- Since the first identified human case in a child in the Democratic Republic of the Congo (DRC) in 1970,^{1,3} human monkeypox has been reported in a number of countries in Central and West Africa, in particular the DRC and Nigeria.⁴ Countries endemic for monkeypox are: Benin, Cameroon, the Central African Republic, the DRC, Gabon, Ghana (identified in animals only), Ivory Coast, Liberia, Nigeria, the Republic of the Congo, Sierra Leone, and South Sudan.¹ Two clades of monkeypox virus have been identified: the West African clade and the Congo Basin (Central African) clade.¹ Although the name of the virus suggests that monkeys are the usual animal reservoir of the virus, evidence of infection with monkeypox virus has been found in many different animal species (including monkeys), and rodents are believed to be the likely natural reservoir of the virus.³
- Human monkeypox cases are increasingly reported in West and Central Africa, likely due to increased exposure to infected animals as a result of deforestation, conflict and displacement, waning immunity from smallpox vaccination, a growing population unimmunized against smallpox, as well as improved surveillance and laboratory capacity in the African region.^{5,6}
- The first occurrence of monkeypox outside the endemic area in Africa was in 2003,⁷ with 47 confirmed and probable human cases in the United States (US) infected via close contact with pet mammals (mainly rodents) carrying the virus. The probable source of the outbreak was attributed to the importation of small mammals from Ghana to Texas, with further spread to other states via pet prairie dogs housed with the infected rodents. No further human-to-human transmission was identified in this outbreak.^{8,9}

- From January 1 – June 15, 2022, 2,103 laboratory confirmed cases of monkeypox were reported to the World Health Organization (WHO) from 42 countries in five WHO regions, with most of these (98%) reported since May, 2022. Most confirmed cases (84%; n=1,773) were reported from the WHO European Region, and 12% (n=245) were from the Region of the Americas (which includes Canada). Of those cases with demographic information available (n=468 cases), 99% of cases were men, with a median age of 37 years.¹⁰ As the global monkeypox outbreak has evolved, WHO has removed the distinction between endemic and non-endemic countries wherever possible in order to highlight the need for a unified response to the outbreak.¹¹
- In Canada, a total of 210 confirmed cases were reported from May 18 – June 22, 2022.^{8,12} This large number of confirmed cases of monkeypox in a short duration of time with no direct travel links to a monkeypox endemic area is unusual, and suggests that there may have been undetected community transmission for some time. This has given rise to an urgent need to understand and contain the global outbreak by raising awareness about monkeypox (e.g., to support health care seeking, and early case detection) and undertaking comprehensive case and contact management.

Methods

- A rapid, focused scan of relevant background information and recently updated monkeypox publications from selected public health organizations available as of June 22, 2022 (e.g., the United States Centers for Disease Control and Prevention [CDC]; the United Kingdom Health Security Agency [UKHSA]; World Health Organization [WHO]; the European Centre for Disease Prevention and Control [ECDC]) informed the content outlined below, with review from PHO medical and scientific staff. It is beyond the scope of this document to examine the potential risk of human-to-animal transmission and endemic zoonotic monkeypox in Ontario.

Epidemiology

- Sporadic monkeypox cases and outbreaks among humans outside of endemic areas have been reported. Travel-related cases have been reported in the US in 2021, Singapore in 2019, Israel in 2018 and Benin in 1978.⁴ For outbreaks in non-endemic areas, the source could previously be traced to travel to endemic areas, contact with infected animal or person, or contact with objects contaminated by an infected person:
 - In 2003, 47 confirmed and probable human cases were reported from six states in the US, attributed to having had contact with pet prairie dogs which in turn acquired the infection after being housed near imported mammals from Ghana, including two African giant pouched rats, nine dormice, and three rope squirrels that later tested positive for monkeypox virus by the Centers for Disease Prevention and Control.¹³ A case control study by Reynolds et al. after the outbreak, found that human cases were more likely than controls to have had daily exposure to a sick animal (odds ratio [OR] = 4.0; 95% Confidence Interval (CI): 1.2–13.4), cleaned cages and bedding of a sick animal (OR = 5.3; 95% CI: 1.4–20.7), or touched a sick animal (OR = 4.0; 95% CI: 1.2–13.4).¹⁴ None of the cases in the outbreak were attributed exclusively to person-to-person contact.¹³
 - In September 2018, three cases were identified in the UK, including two who had recent travel histories to Nigeria but were otherwise epidemiologically unconnected, and a health care worker involved in the care of one of the two cases and likely acquired the infection from contact with contaminated bed linen.^{4,15}

- In May and June 2021, three cases were reported in a family in the United Kingdom (UK), with the index case reporting recent travel to Nigeria.^{16,17}
- On May 15, 2022, WHO was notified of four confirmed human cases of monkeypox from the UK.¹⁸ By June 15, 2022, 2,193 lab confirmed cases had been reported from 42 countries across five WHO regions: African, European, the Americas (including Canada), Western Pacific and Eastern Mediterranean.
 - One death associated with monkeypox infection has been reported to date.^{1,19} The deceased was reported to be an adult male in Nigeria.²⁰
 - All cases confirmed by polymerase chain reaction (PCR) have been identified as being infected with the West African clade.¹
 - In a recently released technical briefing (June 10, 2022), the UKHSA noted that the agency had begun sharing genomic data, and that mutations specific to the current monkeypox outbreak clade had been detected when comparing the current outbreak strain in the UK to that from 2018 in the UK. Identified single mutations (27/48 of which were silent), included a small subset of mutations in proteins associated with virus transmission, virulence or interaction with antivirals.²¹ Further assessment is required to assess the impact of these mutations on virus transmission.
 - The extent and chains of transmission have yet to be determined. Given the number of countries across multiple WHO regions reporting cases of monkeypox, it is highly likely that cases will be detected in other countries.¹ The UKHSA has estimated the mean serial interval to be 9.8 days (although with a high degree of uncertainty).²¹
 - Reported cases thus far have no established travel links to endemic areas. Based on currently available information, cases have mainly but not exclusively been identified amongst men who have sex with men, participating in extended sexual networks, in many cases reporting multiple sexual partners.¹ While transmission through sexual contact has not been documented previously,²² the WHO noted that it is not clear what role sexual fluids may play in the transmission of monkeypox (if any),¹⁰ and the ECDC noted that transmission between sexual partners, due to unprotected intimate contact with an infectious person during sex with infectious skin lesions, seems the likely mode of transmission.²³
 - Genome sequencing from a skin lesion swab from a confirmed case in Portugal in May, 2022 indicated a close match with exported cases from Nigeria to the United Kingdom, Israel and Singapore in 2018 and 2019.²⁴ Further investigation is needed to determine the origin and spread of the currently circulating strain of the virus, and whether this may have been circulating undetected in Portugal and elsewhere since 2019.
 - Preliminary phylogenetic analysis of specimens collected in May 2022 from some European countries showed a close relation to each other, providing further evidence of substantial community spread in Europe:
 - A specimen from an individual in Belgium showed close relation to the recently uploaded genome from the outbreak in Portugal.²⁵

- A specimen from an individual in Spain showed close relation to sequences reported by Portugal and Germany.²⁶
- Genomic sequencing of a specimen collected from an individual in Italy (who arrived from Portugal a week prior to specimen collection) showed close relation to the sequences from Portugal.²⁷
- Phylogenetic inference of the sequence from a skin lesion of a German case was also closely related to that from the case in Portugal (May, 2022) I.^{20,28} Subsequent analysis of genome sequences from nine additional cases with specimens collected between May 15 and 17, 2022 showed close relation to the 2022 sequences from the UK, Portugal and the US. These sequences suggest that the 2022 worldwide outbreak most likely has a single origin that is associated with the exportation of monkeypox virus from Nigeria to non-endemic countries (the UK, Israel and Singapore) in 2018 and 2019.
- Isidro et al. detected 50 mutations (single nucleotide polymorphisms) in the 2022 outbreak virus compared to those in 2018 and 2019, which the authors suggested provided evidence that an “evolutionary jump” may have led to a “hyper-mutated virus”.²⁹
- Epidemiologically, international events have also been implicated in seeding the monkeypox virus worldwide. Contact tracing exercises have traced some cases to the Grand Canarian gay pride festival which had up to 80,000 attendants between May 5 and 15, 2022; at least three cases in Belgium have been traced to a large-scale festival in Antwerp between May 5 and 8, 2022; and many cases in Spain have been traced to a single sauna in Madrid.³⁰ At the time of this report, travel histories for the Canadian cases were not available.³¹
- It has also been hypothesized that low-level transmission of monkeypox may not have been detected given the usually infrequent occurrence and lack of awareness among health care providers.³⁰

Clinical Presentation

- Monkeypox infection is usually self-limited, lasting for 2–4 weeks.⁵ Compared to the Central African clade, the West African clade of monkeypox virus is generally associated with less severe disease.³² However, monkeypox infection may be severe in some individuals, such as children, pregnant women or persons with immunosuppression.¹
- The classical clinical presentation of monkeypox usually involves a fever, followed by swollen lymph nodes and then a rash. Prodromal symptoms may also develop, and include chills, myalgia, fatigue, headache, backache,⁴ and sometimes a sore throat and a cough. Within 1-5 days from the onset of fever, a maculopapular rash develops, often beginning on the face, before spreading to other parts of the body. Lesions on oral or ophthalmic mucosa (enanthem) may be present⁵ and many cases (70%) typically develop a rash on the palms of the hands and soles of the feet.³ Within 12 days, the lesions usually progress sequentially from macules to papules, vesicles, pustules, crusts and scabs.³ The lesions may be centrally depressed and can be extremely itchy.³³ Monkeypox by the West African clade may have very few lesions.⁵ Not often seen in smallpox or varicella is lymphadenopathy, which may be generalized or localized to several areas (e.g., neck, armpit, or groin). Lymphadenopathy typically occurs with fever onset, 1–2 days before rash onset, or less commonly at the time of rash onset.³³

- The clinical case presentation described as part of the current global monkeypox outbreak has been atypical and differs from the classical presentation. The reason for this is currently unknown. Some cases have developed only a few lesions or a single lesion, and many cases have reported that lesions have been limited to the genital or perineal/perianal area. In some instances, the onset of lesions has occurred prior to the onset of fever and other symptoms.¹⁰ The reported high prevalence of genital lesions is believed to be indicative of transmission of the virus occurring from direct contact with infectious skin or lesions during intimate contact.³⁴
 - Data from the 2003 US monkeypox outbreak reported that individuals with exposure to infected animals that resulted in a break in skin (n=6) may not develop a febrile prodrome.⁸ The number of cases may limit the generalizability of this finding to other types of exposure (e.g., person-to-person transmission via skin lesions).
- In a preliminary pooled analysis, combining data from six recent monkeypox clusters reported as part of the current global outbreak (2022):³⁵
 - Detailed information was obtained from 35 cases of a possible 124 cases associated with 1 of 6 clusters in Italy, Australia, the Czech Republic, Portugal and the United Kingdom. Most cases were male, with over half of these in their thirties (54.29%). Cases reported an atypical clinical presentation, including anogenital lesions (31.43%) and cervical lymphadenopathy (11.43%). The predominant reported symptoms among cases was a fever (54.29%) followed by inguinal lymphadenopathy (45.71%). Risk factors for infection included being a young male, having sex with other men, engaging in condomless sex, and a history of previous sexually transmitted infection.
- In a recently released joint surveillance bulletin from the ECDC and WHO (June 22, 2022), summarizing available clinical, demographic and other information from 2,475 cases of monkeypox reported from the WHO European region up to June 21, 2022:³⁶
 - Of 660 cases from the WHO European Region who reported one or more type of symptom, most (n=645, 97.7%) reported a rash (any type).
 - Other common symptoms included skin or mucosal lesions (excluding oral or anogenital lesions; n=504, 76.4%), systemic symptoms (including fever, fatigue, muscle pain, vomiting, diarrhea, chills, sore throat and headache; n=471, 71.4%), and anogenital dermatological skin/mucosal lesions (n=465, 70.5%).
 - Fewer than half of cases reported localized lymphadenopathy (n=325, 49.2%), generalized lymphadenopathy (n=61, 9.2%), oral dermatological skin/mucosal lesions (n=49, 7.4%), respiratory (n=34, 5.2%) or other symptoms.
- While some animals can carry monkeypox virus without symptoms,⁷ there is currently no data on asymptomatic monkeypox in humans. As current testing guidelines in Canada and elsewhere only recommend testing of individuals who have one or more symptoms of monkeypox,^{3,37,38} the true incidence of asymptomatic monkeypox (if any) and its potential transmissibility are currently unknown.

Disease Severity

- The severity of monkeypox can depend upon:
 - The strain of the infecting virus. The West African clade which typically circulates from western Cameroon to Sierra Leone seems to cause less severe illness with a case-fatality rate of 3.6% (95% CI: 1.7%–6.8%), compared to the Congo Basin clade which typically circulates from central and southern Cameroon to the DRC with a case-fatality rate of 10.6% (95% CI: 8.4%–13.3%).³⁹
 - The route of exposure. Data from 47 confirmed and probable cases in the 2003 US outbreak revealed:⁸
 - A higher risk of hospitalization in individuals whose exposure included a break in the skin: 11/17 (68.8%) compared to those whose exposure did not result in a skin break: 3/30 (10.3%); $P < 0.001$.
 - A higher risk of experiencing at least six systemic symptoms in individuals whose exposure included a break in the skin: 8/17 (49.1%) compared to those whose exposure did not result in a skin break: 5/30 (16.7%); $P < 0.041$.
- Complications reported in endemic areas include encephalitis, septicemia, secondary skin bacterial infections (from scratching), vomiting, diarrhea, dehydration, conjunctivitis, keratitis, and pneumonia.^{5,40} In addition, low mood and emotional lability (may be due to monkeypox or being put on isolation), as well as slow-healing skin lesions/ulcers were reported in cases in the UK.⁴¹
- Data on monkeypox in immunocompromised patients are limited—in the 2017 Nigeria outbreak, 2/8 patients with laboratory investigations tested positive for human immunodeficiency virus (HIV) ($n=2$) and they developed > 100 skin lesions associated with genital ulcers. One of the HIV-positive patient had thrombocytopenia. No deaths were reported among HIV-positive patients.⁴²
- Data from 34/37 confirmed monkeypox cases in the 2003 US outbreak noted:⁴³
 - No patients died as a result of monkeypox.
 - 9/34 (26%) required hospitalization > 48 hours, including a patient with hepatitis C who recovered without significant sequelae.
 - 5/34 (15%) developed severe disease (defined by acuity and burden of fever and rash), including:
 - A 6-year-old girl in intensive care who was intubated and put on mechanical ventilation for encephalitis.
 - A 10-year-old girl in intensive care with tracheal airway compromise secondary to a large retropharyngeal abscess and cervical lymphadenopathy.
 - One patient developed keratitis and corneal ulceration and required corneal replacement.

- Pediatric patients (≤ 18 years of age; $n = 10$) were more likely to require intensive care ($p = 0.02$) but not more likely to have fever $\geq 38.3^{\circ}\text{C}$ ($p = 0.70$); fever lasting ≥ 7 days ($p = 0.63$); cervical lymphadenopathy ($p = 1.00$); hospitalization > 48 hours ($p = 0.42$); rash comprised of > 100 lesions ($p = 0.32$).
- Prior smallpox vaccination ($n = 7$; median age = 39 years [range 33–47 years]) was not associated with fever (temperature $\geq 38.3^{\circ}\text{C}$) ($p = 0.62$); fever lasting ≥ 7 days ($p = 1.00$); intensive care ($p = 1.00$); cervical lymphadenopathy ($p = 0.67$); hospitalization > 48 hours ($p = 1.00$); or rash comprised of > 100 lesions ($p = 1.00$).
- On multivariate analysis, nausea and/or vomiting was associated with hospitalization > 48 hours (OR = 15.8; 95% CI = 2.3–106.2; $p = 0.005$).
- In a systematic review of the epidemiology of human monkeypox:³⁹
 - From the 1970s to 1999, 47 deaths were reported; all (100%) occurred in children under 10 years of age in Africa (45 in the DRC and 2 in Gabon). The exact causes of death were not reported.
 - Between 2000 and 2019, 18 deaths were reported (1 in Cameroon, 3 in the Central African Republic, 1 in the DRC, 9 in Nigeria, 4 in the Republic of the Congo); 6 (37.5%) out of 16 with age information occurred in children < 10 years of age. No deaths were reported among the 51 cases in non-endemic areas. The mean age of the seven deaths among the 122 confirmed or probable cases in the 2017 Nigerian outbreak was 27 years.
- In a recently released joint surveillance bulletin for Europe from the ECDC and WHO (June 22, 2022):
 - A total of 2,746 cases of monkeypox were identified via international health reporting mechanisms up to June 21, 2022, with cases reported from 29 countries and areas throughout the European region. Data for a total of 1,799 of these were reported through the European Surveillance System (TESSy).³⁶ Of those cases with a known HIV status, 40.9% ($n=115/281$) were HIV-positive. No deaths were reported among cases.
 - To date during the current global monkeypox outbreak (January 1 – June 21, 2022), a single death has been reported. The death was reported to have occurred in a 40 year old male in Nigeria. The deceased was reported to have a co-morbidity and to be receiving immunosuppressive drugs at the time of his death.²⁰ It is unclear if this individual was classified as a confirmed or probable case of monkeypox.

Transmission

Incubation Period

- The incubation period for monkeypox is usually 6 to 13 days (with a range from 5 to 21 days).⁴⁴
- A recent technical briefing from the UKHSA (June 24, 2022) estimated the mean incubation period to be 9.22 days, after adjusting for factors such as interval censoring, right truncation and epidemic phase bias.⁴⁵
- A recent study by Miura et al., (2022) assessing the reported exposure and symptom-onset dates of 18 confirmed cases detected in the Netherlands in May 2022, found that the mean incubation period was 8.5 days, ranging from 4.2-17.3 days. The authors noted that their findings underscored the importance of a 21 day monitoring period for close contacts of confirmed cases.⁴⁶

Period of Communicability

- The infectious period of monkeypox generally starts with the onset of rash, and until all scabs have fallen off and new skin has grown in, although transmission of monkeypox virus may take place during the prodromal period.^{4,5,33}
- In a retrospective study of seven human monkeypox cases acquired via travel to Nigeria (n=4) as well as locally (n=2 household members) and nosocomially (n=1) in the UK between 2018 and 2021, the authors reported prolonged viremia (viral DNA remained detectable by polymerase chain reaction up to 29 days from rash onset) and upper respiratory tract viral shedding after crusting of all cutaneous lesions (viral DNA remained detectable by polymerase chain reaction up to 41 days from rash onset).⁴¹
- Asymptomatic monkeypox transmission is not known to occur.

Routes of Transmission

- While various animal species have been identified as susceptible to monkeypox virus, uncertainty remains on the natural history of the monkeypox virus and further studies are needed to identify the exact reservoir(s) and how virus circulation is maintained in nature. Currently, rodents are believed to be the most likely natural reservoir of the virus in endemic areas.³
- Humans can be infected with monkeypox virus by being bitten or scratched by an infected animal, by eating inadequately cooked meat or using products from an infected animal.¹
- Unlike the Central African clade of monkeypox virus, for which person-to-person spread is well documented, the West African clade of monkeypox virus is typically associated with limited person-to-person spread³³ (see [Secondary Attack Rates](#) below). Person-to-person transmission of monkeypox may occur through:^{4,5,32}
 - Respiratory tract secretions (e.g., saliva, respiratory droplets) during direct and prolonged face-to-face contact, or during intimate physical contact. Transmission via short-range aerosols may theoretically be possible; however, transmission during the current global outbreak is believed to primarily be occurring via contact with lesions and their fluid, often through intimate/sexual contact.¹⁹

- Spillage or aerosolization of virus-containing specimens by laboratory workers when appropriate biosafety procedures are not followed.
- Contact of non-intact skin or mucous membranes with the body fluids, infectious rash, lesions or scabs of an infected person, or by touching items or surfaces (e.g., bedding or clothing) contaminated with the virus.
- Transplacental transmission from mother to fetus.
- The potential role of sexual fluids in monkeypox transmission is currently unknown.
- In the 2017 Nigeria monkeypox outbreak, Ogoina et al. described >100 skin lesions associated with monkeypox ulceration affecting the genitalia of two patients with monkeypox co-infected with HIV, postulating the potential for monkeypox transmission via close physical contact or genital secretions. However, the authors noted that the role of genital secretions in monkeypox transmission has not been established.⁴²
- Several recent articles have assessed the potential for poxviruses to be transmitted from person to person via genital excretions, and specifically via semen.³⁵
 - In a pre-print pooled data analysis from four recent monkeypox clusters associated with the ongoing global monkeypox outbreak, Bragazzi et al. (2022) noted the atypical clinical presentation among cases compared to previous outbreaks. Most cases reported anogenital lesions and rashes, suggesting that sexual intercourse may play a role in virus transmission.
 - Similarly, a recent rapid communication by Antinori et al. (2022), reviewing the epidemiological, clinical and virological characteristics of four recent cases of monkeypox in Italy, reported that monkeypox viral DNA was detected in the seminal fluid of all three cases from whom seminal fluid was analyzed. While the authors noted that detection of the virus in semen was not necessarily indicative of infectivity, further research regarding the potential role of genital excretions in virus transmission is warranted.⁴⁷
 - In a pre-print case series examining the clinical and virological features of 2 human cases of monkeypox in Germany, Noe et al (2022) noted that monkeypox virus was detected by PCR in specimens from patient pustules, blood and semen. Viral DNA concentrations in semen were comparable to that in the patients' blood, while the virus was not detected in urine specimens from either patient.⁴⁸ The highest concentrations of the virus were detected from swabs taken from the pustules of each patient.
- In a recently released joint surveillance bulletin from the ECDC and WHO (June 22, 2022), summarizing available clinical, demographic and other information from 2,475 cases of monkeypox reported from the WHO European region up to June 21, 2022.³⁶
 - A summary of 75 specimen types testing positive for monkeypox found that the virus was most commonly detected in lesions swabs (n=42, 56.0%), followed by oropharyngeal swabs (n=17, 22.7%), lesion crust (n=8, 10.7%) and rectal swabs (n=7, 9.3%). Monkeypox was detected in a single urine specimen (n=1, 1.3%) and was not detected in serum, semen or genital swabs.³⁶

Secondary Attack Rates

- Person-to-person transmission of monkeypox may be more efficient for the Central African clade of the virus.
- In a systematic review by Bunge et al., the overall secondary attack rates (SARs) of monkeypox ranged from 0% to 10.2%, including:³⁹
 - Among household members:
 - 0% (0/20 contacts) in Cameroon where both Western and Central African clades have been detected.
 - 7.5% (3/40 contacts); median of 50% (range = 50%–100%; contacts of 16 households) in the DRC where primarily Central African clade circulates.
 - Contacts of unspecified nature in areas where primarily the Central African clades:
 - 0% (0/33 contacts) in Central African Republic.
 - 0% (0/30 contacts of one case); 3% (69/2,278 contacts); 3.3% (4/123 contacts); 10.2% (4/39 contacts) in the DRC.
 - 0.3% (1/292 contacts) in Gabon.
 - Contacts of unspecified nature in areas where West African clade is assumed to circulate:
 - 0% (0/16 contacts) in Israel.
 - 0% (0/7 contacts) in Ivory Coast.
 - 0% (0/44 contacts; 0/23 contacts; 0/136 contacts) in Liberia.
 - 0% (0/30 contacts; 0/16 contacts) in Sierra Leone.
 - 0.3% (1/288 contacts) in the UK.
- Using active surveillance data of 338 monkeypox cases and their 3,686 close, face-to-face contacts in Zaire from 1981 to 1986, the observed SAR was 3% (69/2,278 contacts):⁴⁹
 - SARs were significantly higher for contacts unvaccinated against smallpox compared to vaccinated contacts: 7.47% (54 cases/723 contacts) vs. 0.96% (15 cases/1,555 contacts); $p < 0.001$
 - SARs were significantly higher for household contacts compared to non-household contacts: 3.73% vs. 1.86%; $p < 0.05$
 - SAR for household contacts unvaccinated against smallpox was 7 times higher than that for vaccinated household members: 9.28% (40 cases/431 contacts) vs. 1.31% (13 cases/989 contacts); $p < 0.01$

Diagnosis

Please refer to [PHO's website on monkeypox virus](#) for details on testing indications, specimen requirements, how to collect and submit specimens, preparation prior to transport, requisition form and instructions for completion, kit ordering, turnaround time, test methods, and result reporting.⁵⁰

Case and Contact Management

A jurisdictional scan of publicly available information up to June 22, 2022 was completed for select health organizations (i.e., ECDC, CDC, WHO, and UKHSA). This scan was informed by scanning of key health organization websites, as well as general Google searches for items related to case and contact management guidance surrounding monkeypox. A formal bibliographic search was not conducted due to time constraints; thus, some relevant articles may not be included.

Approaches to contact management by selected organizations are summarized below.

World Health Organization

- Investigation of suspect cases should take place as soon as possible and include: clinical examination with appropriate personal protective equipment; exploring possible sources of infection; collecting and submitting specimens for laboratory analysis in a safe manner. For suspected, probable, and confirmed cases definitions, see *WHO's Surveillance, case investigation and contact tracing for monkeypox*, document. A single case of monkeypox in a non-endemic area is considered an outbreak.⁵¹ Given the atypical clinical presentation reported by cases during the current global monkeypox outbreak, WHO recommends that health care providers, particularly in affected communities, should be aware of the signs and risk factors associated with monkeypox, and that any individual meeting the suspect case definition for monkeypox should be offered testing.¹⁰
- Contact definition: A contact is defined as a person who, in the period beginning with the onset of the source case's first symptoms, and ending when all scabs have fallen off, has had one or more of the following exposures (face-to-face exposure; direct physical contact, including sexual contact; contact with contaminated materials such as clothing or bedding) with a probable or confirmed case of monkeypox.^{1,52}
- Contact identification: Cases can be prompted to identify contacts across a number of contexts and any recalled interactions. Attendance lists can also support identification. As soon as a suspect case is identified, contact identification and contact tracing should be initiated. Case patients should be interviewed to elicit the names and contact information of all such persons. Contacts should be notified within 24 hours of identification.¹
- Contact monitoring: Contacts should be monitored at least daily for the onset of signs/symptoms for a period of 21 days from the last contact with a confirmed or probable case or with their contaminated materials during the infectious period.¹
 - Passive: identified contacts provided with information on the signs/symptoms to monitor, permitted activities, and how to contact the public health department if signs/symptoms develop.
 - Active: public health officials are responsible for checking at least once a day to see if a person under monitoring has self-reported signs/symptoms.

- Direct: variation of active monitoring that involves at least daily either physically visiting or visually examining via video for signs of illness.

European Centre for Disease Prevention and Control

- Cases should be assessed medically for severity and risk factors to ensure they receive proper medical care; remain in isolation (including abstaining from sexual activity and close physical contact) until complete healing of rash; contact with immunocompromised persons and with pets should be avoided. See ECDC's [Rapid risk assessment: monkeypox multi-country outbreak](#) for definitions of probable and confirmed cases.⁵
- ECDC definition of a contact of a monkeypox case: sexual partners; persons living in the same household; persons sharing clothing; persons sharing closed workplaces within 1 to 2 metres for long periods of time, caregivers of cases with symptoms, health care workers exposed to monkeypox case body fluids, lab staff with occupational exposure, co-passengers on transit seated 1 to 2 seats apart for at least 8 hours duration.⁵
- Contact management guidance: careful benefit/risk assessment regarding the need for smallpox vaccination [as post-exposure prophylaxis]; self-monitor for 21 days from last exposure for fever or other symptoms (headache, back ache etc.) or new unexplained rash, and if these develop, self-isolate and abstain from sexual activity and avoid close physical contact for 21 days or until monkeypox is excluded; careful hand hygiene and respiratory etiquette; avoid contact with mammalian pets for 21 days or until monkeypox is excluded.⁵
- Description of all other contacts: brief social interactions, work colleagues not sharing same office, person sharing fitness equipment, social encounters, health care workers with appropriate personal protective equipment.⁵
 - Management guidance: Depending on the certainty of contact, some of these contacts may be asked to self-monitor for fever or other symptoms (headache, back ache etc.) or a new unexplained rash for 21 days from the date of last exposure.⁵

United Kingdom Health Security Agency

- Laboratory-confirmed cases should be managed as a high consequence infectious disease for complete containment. See UKHSA's *Guidance: monkeypox: case definitions for definitions of possible, probable and confirmed cases* document.⁵³
- Recommendations for post-exposure prophylaxis depend on the risk of exposure:⁵⁴
 - Individuals deemed to be at medium to high risk of exposure are recommended to be offered post-exposure prophylaxis, ideally within 4 days and up to 14 days following exposure. These individuals should be actively monitored for symptoms daily for 21 days after the date of last exposure, and contact with immunocompromised people, pregnant women, children <12 years of age should be avoided whenever possible. Individuals who have had a high risk exposure are recommended to self-isolate (including work exclusion) for 21 days from the date of last exposure.
 - Protected or droplet exposure, as well as exposures that do not involve physical contact are deemed to be low risk; post-exposure prophylaxis is not required. These individuals can continue with their routine activities and be monitored passively as long as they remain asymptomatic.

Centers for Disease Prevention and Control (CDC)

- See CDC's Monkeypox: case definition for definitions for person under investigation; possible, probable, confirmed orthopoxvirus and confirmed monkeypox cases.⁵⁵
- The CDC recommends that people who have been exposed to animals or people confirmed to have monkeypox should be monitored for fever ($\geq 38^{\circ}\text{C}$); chills; new lymphadenopathy; or new skin rash for 21 days after their last exposure. Fever and rash occur in nearly all individuals infected with monkeypox virus. CDC recommendations for exposed health care professionals include:⁵⁶
 - Any health care worker who has cared for a patient with monkeypox should be alert to the development of symptoms that could suggest monkeypox infection, especially within the 21 day period after the last date of care, and should notify infection control, occupational health, and the health department to be guided about a medical evaluation.
 - Health care workers who have unprotected exposures (i.e., not wearing personal protective equipment) to patients with monkeypox may be at high or intermediate risk of exposure (see CDC's Monkeypox: monitoring people who have been exposed for detail.)⁵⁶ These workers do not need to be excluded from work duty, but should undergo active surveillance for symptoms, which includes measurement of temperature at least twice daily for 21 days following the exposure. Prior to reporting for work each day, the health care worker should be interviewed regarding evidence of fever or rash. Those at high risk of exposure should be offered post-exposure prophylaxis, and those at intermediate risk of exposure should make an informed clinical decision after assessing the risk and benefits of post-exposure prophylaxis.
 - Health care workers who have cared for or otherwise been in direct or indirect contact with monkeypox patients while adhering to recommended infection control precautions are at low or uncertain risk of exposure. Post-exposure prophylaxis is not required and these workers may undergo self-monitoring or active monitoring as determined by the health department.

Considerations for Case and Contact Management

- Ontario has adopted a cautious approach to public health management of suspect, probable and confirmed cases of monkeypox and their contacts. Please see the Ministry of Health *Recommendations for the management of cases and contacts of monkeypox in Ontario* document (as current) for details.⁵⁷

Post-Exposure Prophylaxis

- As monkeypox is related to the virus causing smallpox, vaccines designed for smallpox will provide a degree of cross-protection.⁵⁸ Previous data from Africa suggests that previous vaccines against smallpox may be up to 85% effective in preventing monkeypox infection.⁵⁴
- Imvamune® (Bavarian Nordic A/S) vaccine is a third generation smallpox vaccine authorized in Canada for adults 18 years and older for prevention of monkeypox infection.
 - Imvamune vaccine is produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), an attenuated non-replicating orthopoxvirus.
 - The primary vaccination schedule in vaccinia-naïve individuals consists of two doses of 0.5 mL four weeks apart administered by the subcutaneous route.
 - Preclinical studies and phase I/II clinical trials of Imvamune vaccine have suggested that two doses of vaccine are immunogenic, generating antibody levels considered protective against smallpox, and by extrapolation, monkeypox.
 - A 2019 phase III efficacy trial found that Imvamune vaccine induced peak neutralizing antibodies 2-fold higher compared to a second-generation smallpox vaccine produced by Sanofi Pasteur. Immune responses were shown to be non-inferior after vaccination with a single dose of Imvamune vaccine, at a time when the second-generation vaccine was reported to have induced a protective response.⁵⁹
 - Data on long-term immunogenicity are lacking, but an additional dose of vaccine given to individuals previously vaccinated with smallpox vaccines (including earlier generation vaccines) should rapidly boost pre-existing immunological memory.⁶⁰
 - First and second generation smallpox vaccines have been associated with severe adverse events, including inadvertent inoculation of vaccine provider, generalized or progressive vaccinia, vaccinia keratitis, post-vaccinial encephalitis, and acute myopericarditis. In contrast, Imvamune has a favourable safety profile compared to older generation smallpox vaccines due to the MVA-BN strain being replication-deficient. The most common side effects include injection site pain, erythema, induration and swelling. The most common systemic reactions observed after vaccination are fatigue, headache, myalgia, and nausea. In clinical trials, cardiac adverse events of special interest (AESIs), such as asymptomatic troponin elevation, abnormal ECG findings, tachycardia, and palpitations, were reported to occur in 1.4% (91/6,640) of Imvamune recipients and 0.2% (3/1,206) of placebo recipients who were smallpox vaccine-naïve; however; none of these individuals were confirmed to have myocarditis, pericarditis, or other cardiac inflammatory disease.

- There are limited data on the use of Imvamune vaccine in special populations including persons under 18 years of age, persons who are pregnant or breast-feeding, and persons who are immunocompromised. Additional risk/benefit discussion is indicated for these persons prior to receiving vaccine as PEP. There is very limited evidence on the effectiveness of Imvamune vaccine as post-exposure prophylaxis.⁶¹ Prompt use of Imvamune vaccine within 4 days from the date of last exposure to the case may prevent the onset of symptoms, whereas PEP given between 4 to 14 days from the date of last exposure may modify the disease course.^{56,62} Imvamune vaccine was previously used in two instances in response to several cases of imported monkeypox in the UK. In 2018, the vaccine was offered as post-exposure vaccination to 17 community contacts with 29% (5) uptake. There was no onward transmission identified among the community contacts. The vaccine was also offered to 147 occupational contacts with 85.8% (126) uptake; following post-exposure prophylaxis, one case was identified in a HCW who received vaccine 6 to 7 days after initial exposure. After a separate monkeypox exposure in 2019, 17 of 18 contacts accepted post-exposure vaccination; UKHSA did not report any secondary cases. Infants and young children received post-exposure vaccine in these incidents with no adverse events.
- In response to the current monkeypox cases occurring in several countries worldwide, a limited number of jurisdictions have issued guidance on the use of Imvamune vaccine as post-exposure prophylaxis for the highest-risk contacts of monkeypox cases.^{5,56,63-66} However, there is variability in how risk levels of contacts are defined.
- The UKHSA (June 21, 2022) recommends that vaccine should be prioritized for those individuals likely to gain the most benefit, taking into consideration the length of time since exposure occurred, and the risk of severe disease.⁶¹ Individuals considered to be at increased risk of severe disease include children under the age of 10 years, pregnant women, and those with compromised immunity.
- Although some countries may have a supply of first generation smallpox vaccines, left over from routine immunization programs (concluded in 1980), these are not recommended to be used for monkeypox pre- or post-exposure prophylaxis as, per WHO, they do not meet current safety and manufacturing standards.⁵⁸ Newly developed second- and third-generation smallpox vaccines, such as Imvamune, are considered to be safer, and to have potential benefit in preventing monkeypox infection. However, their supply may be limited, requiring jurisdictions to prioritize their use for priority populations.⁵⁸
 - The National Advisory Committee on Immunization (NACI) recommends that a single dose of Imvamune vaccine may be offered as post-exposure prophylaxis to individuals with a high risk exposure (as defined by PHAC) to a confirmed or probable case of monkeypox, or who are within a setting where transmission of monkeypox is occurring.⁶⁷ The vaccine should be offered as soon as possible and ideally within four days of the last potential exposure, although it may be considered up to 14 days post-exposure. The vaccine should not be offered to individuals with symptomatic monkeypox, or who are considered suspect, probable or confirmed cases of monkeypox. A second dose of vaccine may be offered 28 days after initial dose administration, if an individual is deemed to have a predictable ongoing risk of exposure and if the individual has not received a live replicating 1st or 2nd generation smallpox vaccine in the past (e.g., the post-exposure dose would be considered a booster dose).

Pre-Exposure Prophylaxis

- A prospective vaccination study to evaluate the effectiveness, immunogenicity and safety of Imvamune in health care workers at risk of monkeypox was started in 2017 in the DRC.⁶⁸ While results of the DRC study are pending, the UK has used Imvamune as pre-exposure prophylaxis for 27 health care workers in the two hospitals caring for two imported monkeypox cases in 2018. No onward transmission identified among the community contacts.⁶⁹
- In May 2022, the Advisory Committee on Immunization Practices in the US issued a recommendation on the use of Imvamune for primary vaccination for laboratory personnel and designated response team members against orthopoxviruses. In addition, Imvamune is recommended in place of a second-generation smallpox vaccine for health care workers who are caring for patients infected with orthopoxviruses based on shared clinical decision making. For workers with ongoing risk of occupational exposure to monkeypox virus (and other more virulent orthopoxviruses), a booster dose is recommended every two years after the two-dose primary series. The authors noted that more studies are needed to inform the duration of protection, and the effectiveness of a single dose should exposure occur before peak immunogenicity is reached.⁶⁰
- NACI recommends that Imvamune vaccine be offered as pre-exposure prophylaxis to individuals at high risk of occupational exposure to orthopoxviruses (including vaccinia and monkeypox) in a laboratory setting. The vaccine is recommended to be administered in two doses, 28 days apart, with a booster dose offered after 2 years if the risk of exposure is ongoing.⁶⁷
- The UKHSA (June 21, 2022) recommends that a single dose of pre-exposure vaccination be prioritized for individuals at high risk of occupational exposure to monkeypox, including laboratory workers handling poxviruses, environmental health workers, and healthcare workers providing care or clinical assessment of cases in various healthcare settings, including in hospitals and at community and sexual health clinics.⁶¹ A second dose of vaccine may be offered to individuals at ongoing risk of exposure to monkeypox. The WHO similarly recommends that pre-exposure prophylaxis be offered to individuals at high risk of occupational exposure.⁵⁸
- WHO advises that mass vaccination is not recommended for outbreaks of monkeypox, although as the outbreak evolves and vaccine supply improves, broader use of vaccines for persons at risk may be warranted if justified by the evidence. Vaccination is not currently recommended by the WHO for the general population at this time, as the risk to the general public is considered to be low; however, this may change if the outbreak is not controlled.⁵⁸

Treatment of Monkeypox

- Treatment of monkeypox virus infections is primarily supportive, however, several antivirals have been approved in various countries for the treatment of orthopoxvirus infections and may have some benefit in treating severe monkeypox infections.⁷⁰
 - Tecovirimat (“TPOXX”) has been approved by the US Food and Drug Administration (FDA) and European Medicines Agency for the treatment of smallpox and to treat monkeypox infections.^{19,71,73} Tecovirimat has been approved by Health Canada for the treatment of human smallpox disease and it can be used off-label for the treatment of severe monkeypox infections.^{5,10,73,74}
 - Brincidofovir (“Tembexa”) or “CMX001”, a prodrug of cidofovir, and an antiviral approved by the FDA for the treatment of smallpox, is not currently approved for use in Canada, the US or the EU for the treatment of monkeypox, due to an absence of data on its effectiveness; however, the CDC is currently developing an Expanded Access Investigational New Drug Protocol (EA-IND) to facilitate its use.⁷²
 - Cidofovir (“Vistide” or “Mar-Cidofovir”), is an antiviral approved in both the US and Canada for the treatment of cytomegalovirus (CMV) retinitis in adult patients with Acquired Immune Deficiency Syndrome (AIDS). While there is no data currently available regarding its effectiveness in treating human monkeypox infection, the antiviral has shown effectiveness against orthopoxviruses both in vitro and in animal studies. While the CDC allows for its use to treat monkeypox in an outbreak, its potential benefit in treating serious monkeypox infection is unknown, and it is not considered suitable as a first line treatment due to its nephrotoxicity and inferior safety profile when compared to Brincidofovir.^{72,75}
- The CDC has also approved the use of Vaccinia Immune Globulin Intravenous (VIGIV) for the treatment of monkeypox and other orthopoxviruses in an outbreak; however, its potential benefit in treating severe Monkeypox infection is currently unknown.⁷² Currently, VIGIV is approved by Health Canada under restricted use to treat severe smallpox vaccine-associated adverse events and in response to smallpox occurring in Canada.⁷⁶

Implications for Public Health Practice

- While historically monkeypox virus, and particularly the West African clade of the virus, did not appear to transmit easily from person-to-person, rigorous surveillance and public health measures will be required to manage this outbreak given the concern that undetected monkeypox might have been circulating worldwide due to the following factors:
 - Occurrence of cases around the world beginning in May 2022 in people without travel history to endemic areas, including 210 confirmed cases in Canada as of June 22 (including 33 cases in Ontario).¹²
 - Increasing incidence in endemic areas.
 - Incomplete knowledge of the extent and network of transmission.
 - Virological evidence of mutations with epidemiological and clinical impacts yet to be determined.

- Lack of immunity against orthopoxviruses in population groups under 50 years of age.
- Lack of specifically defined animal reservoirs with the potential of human-to-animal transmission.
- Lack of evidence regarding the potential role of genital secretions in the transmission of infection from person-to-person.
- Many individuals in Ontario are at risk of monkeypox infection if exposed, due to lack of immunity (or waning immunity among those aged 50 and older); however, most cases to date have been identified within certain population subgroups, such as the MSM community. As the outbreak evolves, additional population subgroups may be impacted. Similarly, although most cases reported to date in Canada have been relatively mild (with few hospitalizations and no deaths reported among cases), prevalence of severe infection may increase if monkeypox infection becomes more prevalent among those at increased risk of severe illness, such as children, the elderly or individuals with compromised immunity. While smallpox vaccine and immune globulin may be offered to individuals deemed at high risk of exposure to monkeypox, there is currently limited data on their effectiveness.
- As of June 12, 2022, diagnostic testing of active monkeypox infection in Ontario is performed at the Public Health Ontario Laboratory (PHOL),³⁸ removing the need for specimens to be sent to the National Microbiology Lab (NML) for testing. The PHOL uses a specific monkeypox PCR assay that is able to detect 2 targets – a generic target able to detect both clades of the virus, as well a target specific to the West African clade of the virus.
- A timely public health response, including proactive non-stigmatizing risk communication articulated in collaboration with key stakeholders and community partners, and a cautious approach to public health case and contact management is important to stop further spread of monkeypox.

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