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SYNTHESIS

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

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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 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 droplets 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.
- 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 in men who have sex with men (MSM) seeking care in primary care and sexual health clinics. Potential factors contributing to this multi-jurisdictional surge in cases globally 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 program following eradication of smallpox.[1]

    - Agent factors, e.g.:

        - Potential for mutations leading to increased transmissibility: 50 single nucleotide polymorphisms in the 2022 outbreak 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.

- Collaboration between human and veterinary public health is needed in view of the potential risk of human-to-animal transmission. It is beyond the scope of this document is to examine potential risk of human-to-animal transmission and endemic zoonotic monkeypox in Ontario.

- The emerging epidemiology, and evidence concerning at risk population, routes of transmission, and disease severity need to be carefully monitored to inform 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] human monkeypox has been reported in a number of countries in Central and West Africa, in particular the DRC and Nigeria.[3] 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]

- 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 of smallpox vaccine, a growing population unimmuned against smallpox, as well as improved surveillance and laboratory capacity in the African region.[4,5]

- The first occurrence of monkeypox outside the endemic area in Africa was in 2003,[6] 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 2003 outbreak.[7,8]

- In May 2022 up to May 27, over 400 confirmed and 97 suspect (including possible, probable, suspect) monkeypox cases have been reported from 28 countries.[9] This unexpected large number of confirmed and suspect cases of monkeypox in a short duration of time with no direct travel links to the monkeypox endemic area is unusual, and suggests that community transmission has been going on for some time undetected. 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 tracing and management.

Methods

- A rapid, focused scan of relevant background information and recently updated monkeypox publications from selected public health organizations available as of May 27, 2022 (e.g., the United States Centers for Disease Control and Prevention [CDC]; the United Kingdom Health Security Agency [UK HAS]; 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.

Epidemiology

- Sporadic monkeypox cases and outbreaks 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.[3] For outbreaks in non-endemic areas, the source could 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 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.[10] A case control study by Reynolds et al. after the outbreak found that cases were more likely than controls to have had daily exposure to a sick animal (odds ratio [OR] = 4.0; 95% 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).[11] None of the cases in the outbreak were attributed exclusively to person-to-person contact.[10]

    - In September 2018, 3 cases were identified in the UK, including two who had a recent travel history to Nigeria but 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.[3,12]

    - In May 2021 and June 2021, 3 cases were reported in a family in the United Kingdom (UK), with the index case reporting recent travel history to Nigeria.[13,14]

- On May 15, 2022, WHO was notified of four confirmed monkeypox from the UK.[15] By May 27, 2022, 500 cases (403 confirmed and 97 suspect) have been reported from 28 countries across four WHO regions: European, the Americas (including Canada), Western Pacific and Eastern Mediterranean.
    - Among the 84 confirmed cases from different regions of the world with hospitalization data, 38 (45.2%) were hospitalized.[9]
    - No deaths associated with these monkeypox infections have been reported to date.[1]
    - All cases confirmed by polymerase chain reaction (PCR) have been identified as being infected with the West African clade.[1]
    - The extent and chains of transmission has yet to be determined as surveillance systems are being put in place. 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]
    - 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 seeking care in primary care and sexual health clinics.[1] While transmission through sexual contact has not been documented previously,[16] 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.[17]
    - Genome sequence from a skin lesion swab from a confirmed case in Portugal indicated a close match with exported cases from Nigeria to the United Kingdom, Israel and Singapore in 2018 and 2019.[18]
    - Preliminary phylogenetic analysis of specimens collected in May 2022 from some European countries showed 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.[19]
        - A specimen from an individual in Spain showed close relation to sequences reported by Portugal and Germany.[20]
        - a specimen from an individual in Italy (who arrived from Portugal a week prior to specimen collection) showed close relation to the sequences from Portugal.[21]
        - Phylogenetic inference of the sequence from a skin lesion of a German case also reveals close relation to a 2022 isolate from Portugal.[22] 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. In addition, 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. However, Isidro et al. detected 50 mutations (single nucleotide polymorphisms) in the 2022 outbreak virus compared to those in 2018 and 2019, which suggested that an "evolutionary jump" may have led to a "hyper-mutated virus".[23]

- Epidemiologically, international events have also been implicated in seeding the monkeypox virus worldwide. Contact tracing exercises have traced some cases to the Gran 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; and many cases in Spain have been traced to a single sauna in Madrid.[24] At the time of this report, travel history for the 26 Canadian cases was not available.[25]

- It has also been hypothesized that low-level transmission of monkeypox may not have been detected given the infrequent occurrence and lack of awareness among health care providers.[24]

Clinical Presentation

- Monkeypox is usually self-limiting, lasting for 2–4 weeks.[4] Compared to the Central African clade, the West African clade of monkeypox virus is generally associated with less severe disease.[26] However, monkeypox may be severe in some individuals, such as children, pregnant women or persons with immune suppression due to other health conditions.[1]

- Within three days from the onset of the prodrome symptoms which include fever, chills, myalgia, fatigue, headache, backache,[3] and sometimes sore throat and cough, a maculopapular rash starts from the site of inoculation and rapidly spreads to other parts of the body. Lesions on oral or ophthalmic mucosa (enanthem) may be present[4] and these develop before lesions appear in other parts of the body. Palms and soles are involved in cases of the disseminated rash, which is a characteristic of the disease. Within 12 days, the lesions usually progress simultaneously from macules to papules, vesicles, pustules, crusts and scabs. The lesions may be centrally depressed and can be extremely itchy.[27] Monkeypox by the West African clade may have very few lesions.[4] 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 rarely with rash onset.[27]

    - 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.[7] 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).

Disease Severity

- The severity of monkeypox can depend upon:

    - The strain of the infecting virus. The West African clade which 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 circulates from central and southern Cameroon to the DRC with a case-fatality rate of 10.6% (95% CI: 8.4%–13.3%).[28]

    - The route of exposure. Data from 47 confirmed and probable cases in the 2003 US outbreak revealed:[7]
        - 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.[4,29] 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.[30]
- 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.[31]
- Data from 34/37 confirmed monkeypox cases in the 2003 US outbreak noted:[32]
    - 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 ≥ 38.3°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 ≥ 38.3°C) (P = 0.62); fever lasting ≥ 7 days (P = 1.00); intensive care (P = 1.00); cervical lymphadenopathy (P = 0.67); or hospitalization > 48 hours (P = 1.00); rash comprised of > 100 lesions (P = 1.00).

- On bivariate analysis, hospitalization > 48 hours was associated with fever ≥ 38.3°C (risk ratio [RR] undefined, P = 0.02); rash comprised of > 100 lesions (RR = 3.7; 95% confidence interval [CI] = 1.5–9.0; P = 0.03); adenopathy (RR undefined; P = 0.03); nausea and vomiting (RR = 6.4; 95% CI = 1.6–25.5; P < 0.01); oral lesions (RR = 4.3; 95% CI = 1.6–11.8; P = 0.01).

- 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:[28]

  - From the 1970's 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 and the author also noted that the mean age of the seven deaths among the 122 confirmed or probable cases in the 2017 Nigerian outbreak was 27 years.

Transmission

Incubation Period

- The incubation period for monkeypox is usually 6–13 days (ranges = 5–21 days).[33]

Period of Communicability

- The infectious period of monkeypox generally starts with the onset of rash until all scabs have fallen off and new skin has grown in, although transmission of monkeypox virus may take place during the prodromal period.[3,4,27]

- In a retrospective study of seven monkeypox 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).[30]

- More studies are required to inform if person-to-person transmission can take place in asymptomatic monkeypox.

Routes of Transmission

- While various animal species have been identified as susceptible to monkeypox virus, the exact reservoir(s) has yet to be determined. 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. Humans can be infected with monkeypox virus from eating inadequately cooked meat and other animal products of infected animals.[1]

- Unlike Central African monkeypox virus for which person-to-person spread is well documented, West African monkeypox virus is associated with limited person-to-person spread[27] (see Secondary Attack Rates below) and may take the following routes:[3,4,26]

    - Respiratory tract secretions during direct and prolonged face-to-face contact (duration of contact not reported). Also, laboratory workers are at risk of acquiring monkeypox from spillage or aerosolization of virus-containing specimens when appropriate biosafety procedures are not followed.

    - Spillage or aerosolization of virus-containing specimens by laboratory workers

    - Contact of non-intact skin or mucous membranes with body fluids of an infected person (including from mother to infant after birth), open rash lesions or scabs, or objects (e.g., bedding or clothing) contaminated with the virus.

    - Transplacental transmission from mother to fetus.

- In the 2017 Nigeria monkeypox outbreak, Ogoina et al. described >100 skin lesions associated with monkeypox ulceration affecting the genitalia of two monkeypox patients 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.[31]

Secondary Attack Rates

- Person-to-person transmission of monkeypox seem to take place more efficient for the Central African clade.

- In a systematic review by Bunge et al., the overall secondary attack rates (SARs) of monkeypox range from 0% to 10.2%, including:[28]

    - 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):[34]
    - 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

- Individuals with compatible clinical and exposure history should be assessed by a health care provider and tested as indicated. Consult with PHO's laboratory if you have any questions regarding testing eligibility.[35]
- 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.[35]

Case and Contact Management

A jurisdictional scan of publicly available information up to May 27, 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. At the time of writing, there was no CCM guidance published from Ontario nor Quebec. The literature will be monitored moving forward.

Approaches to contact management by selected organizations are summarized below.

World Health Organization[1]

- Investigation of suspect case 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. See also WHO's *Surveillance, Case Investigation and Contact Tracing for Monkeypox* for definitions of suspected, probable and confirmed cases.[36]

- 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.

- 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.

- 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 patient or their contaminated materials during the infectious period.

    - 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[4]

- 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.[4]

- 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 1–2 m for long periods of time, caregivers of cases with symptoms, health care workers exposed to monkeypox case body fluids, lab staff suffering exposure to occupational accident, co-passengers on transit seated 1–2 seats apart for at least 8 hours duration.

- Contact management guidance: careful benefit/risk assessment for 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, in that case 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 mammal pets for 21 days or until monkeypox is excluded.

- 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.

    - 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 new unexplained rash for 21 days from last exposure.

United Kingdom Health Security Agency[37]

- 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*.

- Recommendations for post-exposure prophylaxis depends on the risk of exposure:

    - Unprotected direct contact or high risk environmental contact are deemed at high risk; post-exposure prophylaxis should be offered ideally within 4 days up to 14 days. These individuals should be actively monitored for symptoms daily for 21 days after last exposure; self-isolation (including work exclusion) should be carried out or 21 days from last exposure; contact with immunocompromised people, pregnant women, children <12 years of age should be avoided whenever possible.

    - Unprotected exposure to infectious materials are deemed at medium risk; post-exposure prophylaxis should be offered ideally within 4 days up to 14 days, and these individuals should be actively monitored for symptoms daily for 21 days after last exposure. Contact with immunocompromised people, pregnant women, children <12 years of age should be avoided whenever possible. Self-isolation is not required and work exclusion is not necessary unless that involves contact with immunocompromised persons.

- Protected or droplet exposure, as well as exposures that do not involve physical contact are deemed at low risk; post-exposure prophylaxis is not required. These individuals can continue with their routine activities and monitored passively as long as they remain asymptomatic.

Centers for Disease Prevention and Control[38]

- See CDC's *Monkeypox: Case Definition* for definitions for person under investigation; possible, probable, confirmed ortopoxvirus and confirmed monkeypox cases.

- CDC recommends that people who have been exposed to animals or people confirmed to have monkeypox should be monitored for fever (≥ 38°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:

    - Any health care worker who has cared for a monkeypox patient 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.)[38] 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 *Monkeypox Virus: Interim Public Health Case and Contact Management Guidance Considerations for Local Public Health Units* for details.[39]

Post-Exposure Prophylaxis

- As monkeypox is related to the virus causing smallpox, vaccines designed for smallpox will provide a degree of cross-protection. Previous data from Africa suggests that previous vaccines against smallpox may be up to 85% effective in preventing monkeypox infection.[37]

- Imvamune 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.[40]

    - 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.[41]

    - First and second generation smallpox vaccines have been associated with severe adverse events, including inadvertent inoculation, 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 is very limited evidence on the effectiveness of Imvamune vaccine as post-exposure prophylaxis. 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.[38,42]

    - 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.[4,38,43-46] However, there is variability in how risk levels of contacts are defined.

    - 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.

    - Existing guidance on post-exposure prophylaxis do not contain recommendations for use in the context of mass vaccination.

    - Guidance on the use of Imvamune vaccine for post-exposure prophylaxis from the National Advisory Committee on Immunization (NACI) is forthcoming.

- Depending on the availability of resources, ring vaccination strategy may be considered to enhance post-exposure prophylaxis. Ring vaccination involves vaccinating all persons surrounding a confirmed or probable case who could potentially contribute to the chain of transmission. Examples include contacts of confirmed or probable cases, as well as those who are in close contact with those contacts.[47] This strategy was used successfully in the final stages of the smallpox eradication program and to suppress Ebola. However, ring vaccination without effective contact tracing measures may be insufficient to contain an outbreak.[48]

Implications for Public Health Practice

- While historically monkeypox did not seem 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:

    - Presence of 26 cases in Canada as of May 26 (including one case in Ontario).

    - Increasing incidence in endemic areas.

    - Incomplete knowledge of the extent and network of transmission.

    - Occurrence of cases around the world in the month of May in people without travel history to endemic areas.

    - Virological evidence of mutations with epidemiological and clinical impacts yet to be determined.
    - Lack of immunity against poxviruses in population groups under 50 years of age.
    - Lack of specifically defined animal reservoirs with the potential of human-to-animal transmission.

- Although the current outbreak is associated with the less virulent Western Africa clade, a clear overview of the epidemiology and clinical presentations is still missing and monkeypox virus may cause severe disease in certain population groups (e.g., young children, pregnant women, immunocompromised persons).[4] Waning effectiveness of smallpox vaccine in older populations, the lack of treatment for monkeypox, and gap in data on the effectiveness of smallpox vaccine as pre-exposure and post-exposure prophylaxis for immunocompromised individuals together may render Ontarians vulnerable to severe monkeypox disease.
- Diagnostic testing of active monkeypox is currently done at the National Microbiology Laboratory, adding to the turnaround time for case identification and subsequent demand on case management capacity. To reduce turnaround time, PHO laboratory will be reporting negatives as final and positives as “preliminary detection of orthopoxvirus”. Meanwhile, special packaging and handing requirements for testing specimens could pose additional operational challenges in prompt case identification.
- 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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