

## EVIDENCE BRIEF

# Monkeypox Risk Assessment (as of September 19, 2022)

Updated: September 2022

## Key Findings

- In May 2022, monkeypox cases with no direct travel links to monkeypox endemic areas were reported to the World Health Organization (WHO) from over 20 countries, including Europe, the United Kingdom (UK), Canada, and the United States (US).<sup>1</sup> Globally, reported cases have mainly but not exclusively self-identified as gay, bi-sexual, or men who have sex with men (gbMSM).<sup>2</sup> According to the WHO, the number of new cases reported globally has been declining through September 2022 including in Canada.<sup>3</sup>
- Recent phylogenetic research suggests that sub-lineage B.1 is responsible for the current global outbreak and first emerged in Europe in March 2022.<sup>4</sup>
- The epidemiological and clinical features of the 2022 global monkeypox outbreak suggest human-to-human transmission via close contact, including close contact via sexual/intimate contact as the main mode of transmission.<sup>5</sup>
  - Monkeypox virus may spread person-to-person via close contact with respiratory secretions of an infected person and from contact with materials contaminated with the virus, although these modes are not considered significant contributors of monkeypox transmission in the current global outbreak.<sup>6</sup>
  - Asymptomatic transmission of monkeypox is believed to be uncommon, but this is an area of active investigation.<sup>7</sup>
  - Monkeypox DNA (not viral isolates) has been detected in seminal fluid during active infection.<sup>8-10</sup> However, the role of sexual bodily fluids (e.g., semen and vaginal fluids) as a distinct route of monkeypox transmission is currently unclear.<sup>2</sup>
  - Healthcare workers (HCWs) may be at risk of occupational exposure to monkeypox virus if there is unprotected contact with a case.<sup>11-13</sup> The risk of nosocomial transmission is considered to be low if appropriate infection prevention and control measures, including the selection and use of appropriate personal protective equipment (PPE), are followed.
- Following exposure to monkeypox virus, symptoms typically develop within 6 to 13 days (and up to 21 days post-exposure).<sup>1</sup> Scientific evidence from the current global outbreak suggest a median incubation period of 7 days.<sup>14,15</sup>

- During the current global outbreak, some cases have reported an atypical clinical presentation including any of the following: absence of skin lesions, atypical oral lesions, development of a single or few lesions, lesions isolated to the anogenital area, onset of a rash/lesions prior to typical prodromal symptoms, and/or mild or absent prodrome.<sup>2,16,17</sup> Despite a recent decline in monkeypox cases globally and in Canada, public health interventions (e.g., education on personal protective behaviours, surveillance, vaccine programs, case and contact management activities, etc.) are recommended to be continued to minimize the potential for a resurgence of cases and new waves of infection to occur, particularly given the potential for undetected cases to have occurred within impacted communities.<sup>18,19</sup>
- Currently, the risk of monkeypox virus transmission to the general public in Ontario is considered low with a low degree of uncertainty. Within the gbMSM community there is a continuum of risk from low to moderate, with a moderate degree of uncertainty, with greater risk for those with sexual/intimate contact with anonymous or multiple partners. The risk of monkeypox causing severe disease or impacting diagnostic testing in Ontario is low with a low degree of uncertainty. The risk of reinfection is low with a low degree of uncertainty. The risk of monkeypox infection 14 or more days after receiving pre-exposure prophylaxis (PrEP) or after receiving post-exposure prophylaxis (PEP) within 14 days of a known exposure is low with a moderate degree of uncertainty. The overall risk assessment for monkeypox may change as new evidence emerges.

## Scope

To summarize available information and evidence on the monkeypox virus, relevant to the risk of importation and transmission in Ontario.

## Background

Monkeypox is a zoonotic infection with symptoms similar to, but milder than, those caused by smallpox.<sup>1</sup> Monkeypox infection is caused by monkeypox virus (MPXV), an enveloped virus within the *Orthopoxvirus* genus in the *Poxviridae* family.<sup>20</sup> The virus was first discovered in 1958 when outbreaks of a pox-like disease occurred in monkeys kept for research in a Danish laboratory.<sup>1</sup>

Since the first identified human case in a child in the Democratic Republic of the Congo (DRC) in 1970,<sup>1,21</sup> human monkeypox infection has been reported in a number of countries in Central and West Africa, in particular the DRC and Nigeria.<sup>22</sup> Countries considered 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.<sup>1</sup>

Two clades of MPXV have previously been identified: Clade I (formerly the Congo Basin Central African clade) and Clade II (formerly the West African clade).<sup>1,23</sup> Clade II consists of two subclades, Clade IIa and Clade IIb, with the latter primarily responsible for the group of variants detected in the 2022 global outbreak.<sup>24</sup> 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.<sup>21</sup>

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.<sup>25,26</sup>

The first occurrence of monkeypox outside the endemic area in Africa was in 2003,<sup>7</sup> with 47 confirmed and probable human cases in the 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.<sup>27,28</sup>

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.<sup>29</sup> WHO has similarly initiated a public consultation process to rename monkeypox infection as the current name of the disease has been identified as having stigmatizing implications, and potentially hindering public health prevention and control efforts.<sup>30,31</sup>

The National Advisory Committee on Immunization (NACI) recommends that the Imvamune<sup>®</sup> vaccine (a 3<sup>rd</sup> generation smallpox vaccine) be offered as pre-exposure prophylaxis (PrEP) to adults at high risk of occupational exposure to the virus in a laboratory research setting.<sup>32</sup> The vaccine has been shown to offer some cross-protection to other poxviruses, including the monkeypox virus. Updates to current NACI PrEP guidance are expected to be released in September, 2022.

In May 2022, Ontario and other affected provinces/countries began offering Imvamune<sup>®</sup> as post-exposure prophylaxis (PEP) to individuals who were deemed to have had a high risk of exposure to the virus.<sup>33</sup> In June 2022 Imvamune<sup>®</sup> was additionally offered as PrEP to individuals deemed to be at risk of exposure to a case of monkeypox.<sup>33</sup> Ontario is currently using a ring-vaccination strategy that aims to limit illness, ongoing transmission and exportation of the virus to unaffected areas.<sup>33</sup>

There is limited evidence regarding the effectiveness of using smallpox vaccines for PEP following exposure to monkeypox virus, however, studies to assess the effectiveness of vaccine in preventing infection are underway.<sup>34</sup>

On July 23, 2022 the WHO Director-General declared the global monkeypox outbreak a Public Health Emergency of International Concern (PHEIC).<sup>35</sup> On August 4, 2022, the US Department of Health and Human Services (HHS) and the Food and Drug Administration (FDA) declared the monkeypox outbreak in the US a public health emergency.<sup>36</sup>

## Methods

From June 5 to September 19, 2022, Public Health Ontario (PHO) Library Services conducted daily searches of primary and preprint literature using the MEDLINE database (search strategies available upon request). In addition, PHO performed grey literature searches daily using news feeds in the Shared Library Services Partnership. English-language peer-reviewed and non-peer-reviewed (preprint) records from June 5 to September 19, 2022 were reviewed and considered for inclusion in this report. Within scope were articles that described monkeypox virus clinical presentation, epidemiology and transmission in the context of the current global outbreak.

The PHO Library Services team performed comprehensive searches of the peer-reviewed, pre-print, and grey literature to identify literature that specifically explored the incidence of monkeypox virus infection in children in non-endemic countries, the risk of monkeypox virus transmission to HCWs in non-endemic countries, and the potential role of asymptomatic transmission of the virus. Given the limited data on monkeypox prior to the current global outbreak, no date restrictions were applied, with the search including results up to July 20, 2022 (nosocomial infections), July 1 (asymptomatic infection) and July 19 (monkeypox in children).

## Genomic Features

Three distinct monkeypox virus clades have been previously identified (Clade I, Clade IIa, and Clade IIb), representing significant diversity through years of evolution in animal reservoirs. A new sub-clade of IIb has been proposed, based on genomes identified in outbreaks in the United Kingdom, Israel, Nigeria, US, and Singapore between 2017 and 2019 and more recently during the 2022 global outbreak. Researchers have proposed that this sub-clade should receive a distinct name (hMPXV1) given the transmission route associated with this sub-clade in humans is distinct from previous monkeypox virus cases.<sup>37</sup> Within the proposed hMPXV1 sub-clade genetic diversity has been noted, with the base proposed to be denoted as “lineage A” with descendant lineages named A.1, A.2, and A.1.1. The current global outbreak would be denoted B.1 (descendent lineage of A.1.1).<sup>37</sup>

Monkeypox virus lineage B.1 is currently the predominant strain of the virus reported to be detected in North America, Europe, South America and Australia and this lineage includes all monkeypox genomes associated with the current global monkeypox outbreak.<sup>38</sup> The sudden rapid global increase in cases associated with the B.1 lineage of monkeypox virus is believed to be due to a combination of factors, including global susceptibility of individuals due to cessation of smallpox vaccination and potentially waning cross-protective immunity among those who previously received smallpox vaccine.<sup>23</sup>

A recent study by Isidro *et al.* (2022) summarized draft genome sequencing of the current outbreak strain of monkeypox virus, with the viral sequence obtained from a swab collected from a skin lesion of a Portuguese patient in May of 2022. Initial phylogenetic analysis indicated the virus belonged to the clade II of the virus.<sup>39</sup>

In a separate publication, the authors noted that while the 2022 outbreak strain of the virus appeared to be a descendent of strains associated with exportation of the virus from Nigeria in 2018 and 2019, current outbreak cases are tightly clustered with a sub-lineage (lineage B.1) of the exported strain (lineage A.1).<sup>4</sup>

Compared to previous exported strains of the virus originating in endemic countries, the current B.1 outbreak lineage has been found to have close to 50 mutations.<sup>4</sup> This is more than the previously estimated nucleotide substitution rate for *Orthopoxviruses* (1-2 substitutions per genome per year) and may provide evidence of adaptation of the monkeypox virus to humans, and of sustained human to human transmission.<sup>40</sup>

Sequencing of a 2021 case in the US with a history of travel to Nigeria appeared to show that much of the variation between the genome of cases exported from Nigeria in 2018 (lineage A.1) and that of the current outbreak strain (lineage B.1), likely arose from a previous epidemic in Nigeria.<sup>23,41</sup>

Phylogenetic analysis of available monkeypox virus genomes by Luna *et al.* (2022) also found that lineage B.1 includes all monkeypox virus genomes associated with the current global outbreak of the virus, with the B.1 lineage estimated to have emerged in Europe on March 2, 2022 (95% CI: Nov 13, 2021 – May 10, 2022).<sup>23</sup>

Gigante *et al.* (2022) reassessed sequencing data for 206 specimens in the US that were positive for monkeypox virus after observing an unusual WGS profile for a lesion specimen from a particular case.<sup>42</sup> Reassessment identified a further 6 genomes (n=7; 3.4%) with similar abnormal mapped reads, which include gaps and high coverage plateaus.<sup>42</sup> Various genomic deletions were identified within individual sequences, leading the authors to conclude that if such mutations become more widespread, then PCR diagnostic testing that targets non-essential genes may be rendered less or ineffective.<sup>42</sup>

## Epidemiology

As of September 16, 2022, the WHO reported a global total of 60,841 laboratory confirmed cases of monkeypox.<sup>3</sup> Within the Region of the Americas, which accounted for 59.3% of the global case total, the highest number of confirmed cases were reported from the US (n=22,616) followed by Brazil (n=6,448), Peru (n=2,015) and Canada (n=1,338).<sup>3</sup> Minor differences between local case counts and those reported by WHO may occur due to reporting delays.

In Canada, as of September 16, 2022, a total of 1,363 confirmed cases have been reported to the Public Health Agency of Canada (PHAC), with most cases reported from Ontario (48.1%, n=656) and Quebec (37.8%, n=515).<sup>43</sup> The 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.

Given the rapid global emergence of confirmed monkeypox cases in 2022, and the previous rarity of monkeypox infections in non-endemic areas, it is likely that the true number of infections is higher than those currently detected.<sup>19</sup> Confirmed cases of infection may be unreported due to several reasons, including unrecognized infection if cases do not seek diagnosis or treatment, lack of access to testing, or misdiagnosis of infection (particularly early in the outbreak).

A recent publication by Maruotti *et al.* (2022) attempted to estimate the true number of monkeypox infections in those countries that have experienced the highest burden of confirmed cases during the current global outbreak.<sup>19</sup> Utilizing a capture-recapture estimation approach and applying this to cumulative weekly reported infections reported by countries with the 10 highest case counts, the authors estimated the total number of cases that may have occurred in each of these countries up to July 31, 2022.<sup>19</sup> For Canada, the authors estimated that the true number of cases may be 2.24 times

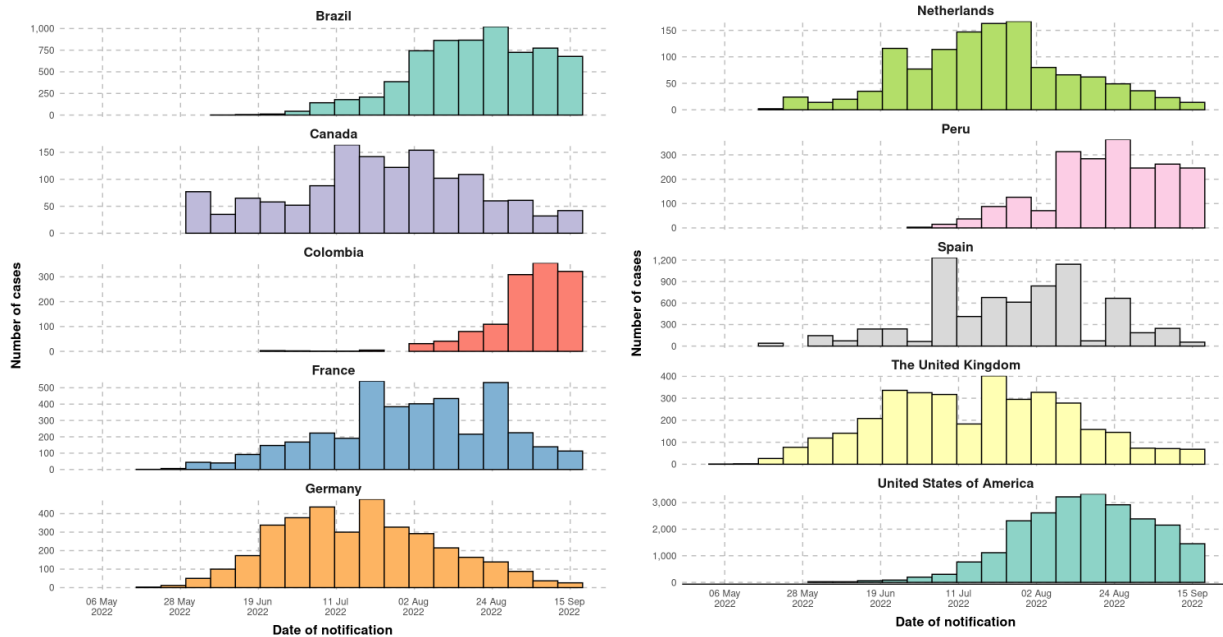
higher than observed.<sup>19</sup> Based on their analyses, the authors estimated that the true number of cases in Canada as of July 24 may have been 1,511 (95% CI: 1,321-1,701), compared to 676 reported cases of monkeypox.<sup>19</sup> While there was some heterogeneity in the ratio of estimated to total confirmed cases (ranging from 1.82-3.16), all countries examined were estimated to have numerous additional cases, with these unrecognized cases having potential implications for contact tracing and outbreak containment.<sup>19</sup> Per recent data from WHO (September 19, 2022), most (but not all) cases reported globally up to September 16, 2022 have been reported among males (97.4% of the n=32,125 confirmed cases with gender information available).<sup>3</sup>

Per the Public Health Ontario (PHO) epidemiological summary (September 13, 2022), most confirmed cases in Ontario are male (n=651, 99.2%), with 5 female cases confirmed to date (0.8%).<sup>44</sup>

Epidemiological updates from the WHO as of September 16, 2022 have noted that the global incidence of monkeypox infection appears to be slowing. The number of new cases reported to WHO dropped by 38.6% for the week of September 12-18, 2022 (n = 2,985) compared to the previous week of September 5 – 11, 2022 (n= 4,863).<sup>3</sup> Within specific WHO regions, the progression of the outbreak is more variable, and based on the total number of confirmed infections to date.

As of September 19, 2022, the top 10 affected countries, in order, have been the US (n=22,957), Spain (n=7,037), Brazil (n=6,649), France (n=3,898), Germany (n=3,563), United Kingdom (n=3,552), Peru (n = 2,054), Canada (n=1,363), Colombia (n=1,260), and the Netherlands (n=1,209). Similar to other countries (see Figure 1 below), Canada continues to experience a decline in confirmed monkeypox case counts (43% decline in the 7-day change in case numbers comparing September 12 – 18 to September 5 to 11).<sup>3</sup>

**Figure 1: Monkeypox epidemic curves for cases from the top 10 affected countries. Note different y-axis scales\***



Source: WHO data as of 17 Sep 2022 17:00 CEST

**Data Source:** World Health Organization. 2022 monkeypox outbreak: global trends [Internet]. Geneva: World Health Organization; 2022 [cited 2022 Sep 21]. 2. Global situation update. 2.5. Epidemic curve – top 10 countries (cases). Available from: [https://worldhealthorg.shinyapps.io/mpx\\_global/](https://worldhealthorg.shinyapps.io/mpx_global/). Licence: CC BY-NC-SA 3.0 IGO.

\*Note: differences in outbreak progression between countries should be interpreted with caution as these are impacted by factors such as local and national differences in case and contact management, case detection and reporting, availability of confirmatory testing, and availability of vaccine via PrEP and PEP. Due to differences in underlying population size and structure, comparison of the number of cases in each country instead of population adjusted rates can also affect interpretation of the true burden of infection in each country.

There have been no occurrences of monkeypox reinfection reported in the scientific literature.

## Monkeypox Virus (in those under 18 years of age)

As of September 16, 2022, among 33,363 monkeypox cases reported with age data to the WHO during the current monkeypox virus outbreak, 0.9% (n=293) were under the age of 18 years, including 86 (0.3%) who were under 5 years of age.<sup>3</sup>

Although cases and outbreaks of monkeypox in non-endemic countries have been reported prior to 2022, including cases among children, these were ultimately attributed to recent travel to an endemic area, or to contact with infected animals imported from an endemic area.<sup>45-47</sup>

- As of September 13, 2022, the European Centre for Disease Control (ECDC) and WHO reported that 0.3% (n=62/23,533) of cases reported from the WHO European Region with available information on age were under the age of 18 years.<sup>48</sup>
- PAHO reported that as of August 4, 2022, 0.6% of reported cases were in individuals under 18 years (96/16,969), with 26% of these (n=25 cases) in children under 5 years.<sup>49</sup>
- In Ontario, as of September 13, 2022, 5 cases under 20 years of age have been reported<sup>44</sup>

Several recent scientific publications have reported incidents of monkeypox infection in children, including those in non-endemic areas. While household exposure may be a source of monkeypox exposure to children in non-endemic areas in the current outbreak, other sources of infection continue to be explored.

## Mode of Transmission

During the current outbreak, transmission from person-to-person appears to be predominantly occurring via direct contact with the infectious rash, lesions or scabs of a person who is infected with the monkeypox virus, during close contact (e.g., intimate or sexual contact).<sup>50,51</sup> While cases reported to date have disproportionately occurred among adult males who self-identify as belonging to the gbMSM community, it is important to note that anyone is susceptible to monkeypox infection, regardless of their gender or sexual orientation.

A recent summary of the global monkeypox outbreak by WHO (2022) specifically examined the mode of transmission among cases reported to date. Among those cases reported to WHO up to September 16, 2022 (including those who identified as gbMSM), a sexual encounter was the most commonly reported mode of transmission (n=10,215, 87.6%), with a party setting with sexual contact reported to be the most common exposure setting (n=3,099, 48.6%).<sup>3</sup> Comparatively, among cases with a known sexual orientation who did not self-identify as belonging to the gbMSM community and for whom transmission data were available, the most commonly reported mode of transmission was also a sexual encounter (n=255, 62.2%), with a party setting with sexual contact also reported to be the most common exposure setting (n=51, 30.7%), followed by within household exposure (n=30, 18.1%).<sup>3,10</sup>

A recent publication by Thornhill *et al.* (2022) similarly assessed case data for 528 individuals diagnosed with monkeypox from April 27-June 24, 2022, and distributed across 16 countries.<sup>14</sup> The authors reported that 98% of infections were in men who self-identified as gbMSM.<sup>14</sup> Transmission of the virus during sexual contact was the predominant reported mode of virus transmission (95% of cases), with a median of 5 sexual partners among those individuals (n=406) with available information on sexual history.<sup>14</sup>



A recent systematic review by Bunge *et al.* (2022) found that the weighted average of the median age of reported cases (including those from both endemic and non-endemic countries) has increased over time.<sup>52</sup> This was found to be 4 years in the 1970s, increasing to 10 years in the 2000s, and more recently to 21 years in the 2010s.<sup>52</sup>

Among confirmed cases reported from Ontario (September 13, 2022), the most commonly reported risk factors reflect those identified by WHO, and include intimate or sexual contact with new and/or multiple partners.<sup>44</sup>

Most cases report a history of close, intimate contact with a person infected with monkeypox. While exposure to respiratory secretions or exposure via contaminated linens or environmental surfaces is also possible, this does not appear to be a common route of transmission.<sup>3</sup> Per the WHO (2022), for those cases for whom transmission data were available, contact with contaminated material was reported to be the route of transmission for 0.2% (n=23) of cases among those who identified as gbMSM, and for 1.6% (n=4) of cases outside of the gbMSM community.<sup>3</sup>

Recently, several instances of monkeypox infection have been reported in Italy and Spain, where individuals are believed to have acquired infection via fomite transmission while receiving a tattoo.<sup>53</sup> In the case of the individual in Italy, initial rash onset occurred at the site of the newly received tattoo, and swabbing of the affected area confirmed monkeypox infection via PCR.<sup>53</sup> These incidents further highlight the need for adherence to good infection prevention and control measures by personal service settings, as a means of prevention for infectious diseases.

Evidence of human-to-dog transmission of monkeypox virus was recently observed in France, with a dog in the same household as 2 individuals with confirmed monkeypox virus subsequently developing signs and symptoms of monkeypox infection, and testing positive for the virus.<sup>54</sup> Ongoing collaboration between human and veterinary public health is needed in view of the potential risk of human-to-animal transmission and establishment of new animal reservoirs.

## Nosocomial Transmission of Monkeypox Virus

HCWs providing care to a person with confirmed monkeypox infection may be at risk of exposure to the virus if appropriate infection prevention and control measures, including the use of appropriate personal protective equipment (PPE), and safe handling of sharps (e.g., needles) are not followed.

## NOSOCOMIAL TRANSMISSION OF MONKEYPOX VIRUS DURING THE CURRENT GLOBAL OUTBREAK

Per the WHO, although cases of monkeypox infection have been reported from individuals who are employed as HCWs (n=415/11,337; 3.7%), most of these individuals likely acquired their infection in the community and not via occupational exposure.<sup>3</sup> A summary by WHO of global cases by transmission type (of those cases with transmission data available), noted that healthcare-associated transmission events were rare (n=5/11,557 events; 0.04%), as were occupational exposures in a laboratory setting (n=4/11,557 events; 0.03%).<sup>3</sup>

Several instances of nosocomial transmission to HCW have been reported during the current outbreak. In each instance where transmission of the virus to HCWs occurred, one or more deviations from infection prevention and control best practices were identified, including a failure to wear all recommended pieces of PPE, direct unprotected contact with potentially contaminated fomites, or exposure to the virus via a needlestick injury.<sup>11,55,56</sup>

Bubach Carvalho *et al.*, (2022) reported on a case of occupation transmission of monkeypox virus to a HCW who was exposed to the virus via a needlestick injury.<sup>56</sup> Although the HCW was wearing appropriate PPE, including gloves, the HCW sustained a needlestick injury to her thumb when a contaminated needle used to collect samples from a cutaneous lesion of a monkeypox patient perforated her glove.<sup>56</sup> The HCW subsequently developed a nodule at the puncture site 5 days after exposure, followed by onset of an additional 6 lesions at other body sites including the hands, thigh and face.<sup>56</sup> No other potential exposures to the virus were identified and both blood and lesion specimens from the HCW were found to be positive for monkeypox virus on PCR testing.<sup>56</sup> Notably, virus was detectable in the HCWs blood 8-days post-exposure and prior to onset of disseminated lesions.<sup>56</sup> The authors concluded that the relationship between detectable monkeypox virus in blood and true viremia is unknown and that a HCW who sustains a potential bloodborne exposure to the virus should receive PEP.<sup>56</sup>

A recent publication by Salvato *et al.* (2022) reported on occupational monkeypox infection in 2 nurses who had visited the home of a suspected case to collect specimens from genital lesions for testing.<sup>55</sup> PCR testing subsequently confirmed monkeypox infection.<sup>55</sup> While both HCWs wore appropriate PPE (gloves, eye protection, and a gown) during specimen collection and packaging, gloves were not used when handling the packaged specimens during transport, and were not worn in the home of the case other than during specimen collection.<sup>55</sup> Items brought into the home, such as a clipboard and the specimen transport box, were not decontaminated.<sup>55</sup> Both HCWs subsequently developed symptoms of monkeypox infection 5 days after visiting the client's home, including lesions on the fingers and/or forearms.<sup>55</sup> Monkeypox infection was confirmed in both healthcare workers via real-time PCR. Based on the nature of exposure and use of appropriate PPE during specimen collection, the healthcare workers were believed to have acquired infection via indirect exposure to contaminated fomites within the client's home.<sup>55</sup>

Marshall *et al.* (2022) examined adherence to recommended PPE guidance among Colorado HCWs deemed to have had an occupational exposure to monkeypox virus.<sup>11</sup> The CDC recommends that HCWs providing direct care to patients with suspected or confirmed monkeypox infection wear a gown, gloves, eye protection and N95 respirator.<sup>11</sup> The authors collected data on 313 HCWs who had direct or indirect exposure to a patient subsequently diagnosed with monkeypox infection from May 1-July 31, 2022.<sup>11</sup> Only 23% of HCWs reported wearing all recommended PPE for interactions with patients with suspected or confirmed monkeypox infection, with compliance reported to be lowest in primary and urgent care settings, and highest in community health and STI clinics.<sup>11</sup> Although 87 HCWs (28%) were deemed to have had an intermediate-high risk exposure requiring PEP, only 7 individuals went on to develop symptoms of monkeypox within the 21 day period following exposure, and none were confirmed to have monkeypox infection.<sup>11</sup> The authors concluded that the risk of occupational exposure to infection in healthcare settings is low, however, HCWs could benefit from educational reminders regarding infection prevention and control measures to be followed during patient interactions, particularly in settings where reported compliance was low.<sup>11</sup>

## NOSOCOMIAL TRANSMISSION OF MONKEYPOX VIRUS PRIOR TO THE CURRENT GLOBAL OUTBREAK

Prior to the current global monkeypox outbreak, sporadic instances of nosocomial transmission of monkeypox virus have been reported. In each instance where transmission of the virus to HCWs occurred, failure to wear one or more recommended pieces of PPE was identified.<sup>12,13,57,58</sup>

A rapid literature review by Zachary & Shenoy (2022) from 2000-2022 identified a single reported case of nosocomial monkeypox transmission in 2018.<sup>12</sup> A HCW without appropriate PPE in the UK was exposed to the virus through contact with patient bedding believed to be contaminated with the virus.<sup>13</sup> At the time of exposure the patient had skin lesions consistent with monkeypox infection, however possible monkeypox infection had not been considered or identified, so only gloves and an apron were worn, but no face mask or respirator when handling the linen.<sup>12,13</sup> The HCW developed signs and symptoms of monkeypox infection approximately 13-15 days post-exposure, despite receiving post-exposure prophylaxis (3<sup>rd</sup> generation smallpox vaccine) 5-7 days post-exposure.<sup>13</sup>

Fleischauer *et al.* (2005) explored HCW exposure to monkeypox virus during the 2003 US outbreak of monkeypox virus associated with contact with infected pet prairie dogs.<sup>57</sup> HCWs were considered exposed to the virus if they had entered a two-metre radius surrounding patients with confirmed monkeypox infection.<sup>57</sup> 54% (n=31) of the HCWs had a prior history of smallpox vaccination.<sup>57</sup> Although 70% of HCWs who participated in the study (n=40) reported having 1 or more unprotected exposures (failure to wear one or more items of appropriate PPE while within 2m of a monkeypox patient), none experienced symptoms of monkeypox virus following exposure.<sup>57</sup> Individual items of PPE were reported by HCWs to be worn for every case encounter with varying frequency (gloves were always worn by 61% (n=35), gown by 33% (n=19), surgical mask by 25% (n=19) and N95 respirator by 19% (n=11)).<sup>57</sup> Paired serological testing for study participants showed that only 1 HCW tested positive via ELISA for anti-orthopoxvirus IgM at both acute and convalescent phases.<sup>57</sup> This may have been attributable to false-positive test results, recent infection, or to this individual having received smallpox vaccine four months prior to the exposure.<sup>57</sup> The authors concluded that in their investigation, the transmission of monkeypox virus to HCWs involved in direct patient care in a healthcare setting was likely rare.<sup>57</sup>

In a retrospective observational study conducted in the UK from 2018-2021, Adler *et al.* (2022), conducted a review of patient charts and identified 7 patients who had been treated for the virus in high consequence infectious disease (HCID) units in the UK during the study period.<sup>58</sup> Four of the cases acquired infection during travel to Nigeria.<sup>58</sup> Three cases including a case in a HCW, were attributed to secondary transmission, including within-household transmission.<sup>58</sup> The infected HCW developed symptoms of monkeypox infection 18 days after occupational exposure to one of the travel-associated cases, despite receiving a single dose of smallpox vaccine as post-exposure prophylaxis on day 6 post-exposure.<sup>58</sup> The infected HCW reported that they had not used PPE during provision of care to the index case.<sup>58</sup>

Costello *et al.* (2022) reported a case of a traveller returning from Nigeria in 2021, who developed symptoms of monkeypox while in transit to the US.<sup>59</sup> The patient was promptly isolated following hospital admission, and both airborne and contact precautions (including use of eye protection) were implemented.<sup>59</sup> Follow-up of HCWs who had contact with the patient found that none of these met the criteria for a high-risk exposure, so post-exposure prophylaxis was not administered.<sup>59</sup> All contacts were actively monitored for signs and symptoms of monkeypox infection for 21 days post-exposure, and none of these became symptomatic.<sup>59</sup> Adherence to infection control measures including case isolation, the

use of PPE by HCWs, contact tracing, and active monitoring of identified contacts, likely prevented secondary transmission of infection in the healthcare facility.<sup>59</sup>

Kyaw *et al.* (2020) outlined the experience of the attending hospital, following the first identified case of monkeypox in Singapore.<sup>60</sup> The patient was exposed to the virus while travelling to Nigeria.<sup>60</sup> Risk assessment of close contacts identified 27 HCWs who had had close contact with the patient, however no instances of nosocomial transmission were identified.<sup>60</sup> All HCWs reported consistent use of gloves and a gown for each potential exposure, however 4 lab technicians reported not using a face mask, and 14 HCWs (3 HCWs with direct patient contact and 11 HCWs who only had contact with the patient's surrounding or specimen) reported not using eye protection.<sup>60</sup>

## Transmissibility

Previously, outbreaks of monkeypox virus in both endemic and non-endemic areas have not demonstrated sustained transmission, with the basic reproductive number ( $R_0$ ) <1, regardless of whether contacts had a prior history of smallpox vaccination.<sup>61</sup>

Endo *et al.* (2022) conducted statistical modelling using current monkeypox outbreak data from the UK and found that the  $R_0$  within sexual contact networks may be higher than 1, which may pose challenges for contact tracing and outbreak containment.<sup>61</sup> Similarly, a pre-print publication from Du *et al.* (2022) aggregated all reported cases from 70 countries up to July 22, 2022 and estimated the  $R_0$  to be 1.29 (95% CI: 1.26, 1.33).<sup>62</sup> The authors noted however, that this aggregated value does not denote the risk for the general population and is more reflective of the risk faced by the gbMSM community, within which most cases to date have occurred.<sup>62</sup>

Betti *et al.* (2022) noted the need for pair formation models to be used when modelling infections such as monkeypox, which are transmitted through close, prolonged contact, and which typically result in immunity following recovery from infection.<sup>18</sup> Applying this modelling approach to data obtained during the current global monkeypox outbreak, and making the assumption that most case to case interactions are casual and short, the authors found that when  $R_0$  is sufficiently large (approaching  $R_0=2$ ), while an initial outbreak of infection may be large, this will likely end relatively quickly as cases recover and develop immunity.<sup>18</sup> Resulting models were fitted to both Canadian and global data.<sup>18</sup> Based on their modelling observations, the authors noted the need for public health measures such as increased surveillance and rapid implementation of control measures to be continued even when the local incidence of cases appears to have decreased, in order to prevent a resurgence of cases and successive waves of infection.<sup>18</sup>

The UKHSA (August 1, 2022) reported that predictive modelling of monkeypox cases in the UK appears to show that the transmission of monkeypox in the UK has slowed, with the current growth in confirmed daily cases estimated to be zero (with some uncertainty).<sup>50</sup>

Predictive modelling by Bisanzio & Reithinger (2022) in simulated populations of 5-50 million residents found that public health control measures such as rapid contact tracing, case detection and isolation, and ring vaccination can effectively reduce both outbreak size and duration.<sup>63</sup>

Yuan *et al.* (2022) similarly found that isolation of  $\geq 65\%$  of symptomatic cases and tracing of 60% of their contacts could greatly reduce the risk of an outbreak.<sup>64</sup>

Behaviour change within the gbMSM community as a result of increased awareness of the ongoing outbreak, and increased vaccine uptake by individuals at risk of exposure to the virus are also likely to have contributed to observed declines in monkeypox incidence in Canada and elsewhere. Recent modelling by Spicknall *et al.* (2022) found that one-time sexual encounters account for roughly half of daily monkeypox virus transmission in the US, and that a 40% reduction in these encounters might reduce the percentage of individuals infected with the virus by up to 31%.<sup>65</sup>

From August 5 – 15, 2022 the American Men’s Internet Survey (AMIS) conducted a monkeypox-specific cross-sectional survey of 824 cisgender men in the US who report having sex with men.<sup>66</sup> The goal of the survey was to assess general knowledge of the virus, monkeypox vaccine uptake, and personal behavioural changes in the previous 3 months due to the outbreak.<sup>66</sup> Most respondents (90%) reported having sex with at least 1 man in the previous 3 months. Almost half of respondents reported changes to their sexual behaviour since learning about the ongoing monkeypox outbreak, including reducing the number of sexual partners (47.8%), reducing group sex participation (50.4%) and reducing one-time sexual encounters (49.8%).<sup>66</sup> Just under a fifth of respondents (18.5%, n=151) had received at least 1 dose of PrEP, with vaccine uptake higher among those who had 2 or more partners in the previous 2 weeks (30.1%) compared to those who reported no or 1 partner in the previous 2 weeks (13.9%).<sup>66</sup>

## Incubation Period

Following exposure to the virus, most people typically develop signs and symptoms of monkeypox infection within 6 to 13 days, however, people may develop symptoms as early as 5 days following exposure and up to 21 days post-exposure.<sup>1</sup> Recent studies have explored the incubation period associated with monkeypox infection during the current global outbreak.

Thornhill *et al.* (2022) summarized information for 528 individuals across 16 countries diagnosed with monkeypox infection from April 27-June 24, 2022. Of those individuals (n=23) with clear exposure history, the median incubation period was found to be 7 days (range 3-20 days).<sup>14</sup>

Tarín-Vicente *et al.* (2022) conducted a prospective observational cohort study across 3 sexual health clinics in Spain.<sup>15</sup> All patients confirmed to have laboratory-confirmed monkeypox infection from May 11-June 29, 2022 (n=181) were enrolled in the study.<sup>15</sup> Various outcomes were assessed by the authors, including exposures, symptoms and the time to symptom onset.<sup>15</sup> The median incubation period among participants was found to be 7 days (IQR: 5-10 days).<sup>15</sup>

## Symptoms

Historically, monkeypox infection typically begins with a prodrome of symptoms such as a fever, headache, chills, swollen lymph nodes and muscle aches before development of a rash that usually starts on the face and then spreads elsewhere on the body.<sup>67,68</sup> The rash can also affect the mucous membranes in the mouth, tongue, and genitalia. The rash may affect the palms of hands and soles of the feet. The rash can last for 2–4 weeks and progresses through the following stages: macules, papules, vesicles, pustules, and scabs.<sup>69</sup> Symptoms are generally mild and resolve within 4 weeks.<sup>69</sup>

During the current global outbreak, many cases have reported an atypical clinical presentation.<sup>2</sup> Atypical presentations have included an absence of skin lesions, proctitis, mild or absent prodrome, atypical oral lesions, development of a single or few lesions, lesions isolated to the anogenital area, and/or onset of a rash/lesions prior to typical prodromal symptoms.<sup>2,14,16,17</sup> The reason for atypical symptom presentation among cases is currently unknown, however, the reported high prevalence of genital lesions may

indicate transmission of the virus via contact with infectious lesions during intimate or sexual contact with an infected individual.<sup>5</sup>

As of September 19, 2022, the WHO has reported that among laboratory confirmed cases experiencing at least one symptom, most cases reported any type of rash (n=19,016; 84.7%).<sup>48</sup> Commonly reported systemic symptoms have included fever (n=12,803; 57.1%), fatigue (n=6,639; 29.6%), headache (n=6,754; 30.1%) and muscle pain (n=6,072; 27.1%).<sup>3</sup> Less common symptoms (i.e., reported by <10% of cases who reported at least 1 symptom) included an oral rash (n=1,963; 8.7%), chills (n=1,461; 6.5%), vomiting (n=444; 2.0%) or conjunctivitis (n=99; 0.4%).<sup>3</sup> Asymptomatic infection among laboratory confirmed cases was rarely reported (n=16; 0.1%).<sup>3</sup>

Predominant symptoms reported by Ontario cases (September 13, 2022) include a rash (n=518, 77.8%), 1 or more oral/genital lesions (n=407, 61.1%) and/or a fever (n=322, 48.3%).<sup>44</sup>

## Disease Severity

While all individuals are susceptible to monkeypox infection, certain individuals are at higher risk of severe symptoms and outcomes due to monkeypox infection, including newborn infants, young children, pregnant women, and individuals who are immunocompromised.<sup>70</sup>

Historically, the case fatality rate associated with the clade II of monkeypox virus is 0-11%, with young children at increased risk of death due to monkeypox infection compared to adults.<sup>6</sup> More recently, the case fatality rate has been estimated at 3-6%.<sup>6</sup>

As part of the current global outbreak, WHO has reported a total of 23 deaths as of September 16, 2022 (n=14 African Region, n=4 Region of the Americas, n=3 European Region, n=1 Eastern Mediterranean Region, n=1 South-East Asia Region).<sup>3</sup> Within the Region of the Americas, reported deaths have occurred in Brazil (n=2), Ecuador (n=1) and Cuba (n=1).<sup>3</sup> No deaths have been reported from Canada.<sup>3</sup> According to US news media (September 13, 2022), a single death due to monkeypox in an individual with compromised immunity has been confirmed in the US, however, this incident is not yet reflected in WHO reporting.<sup>71</sup>

The ECDC and WHO jointly reported that 0.08% (5/6,296) of confirmed cases in the WHO European Region required admission to intensive care units (ICUs).<sup>48</sup>

In Ontario, as of September 13, 2022, 2.9% of cases (n=19) have been hospitalized and 0.3% (n=2) have been admitted to the ICU.<sup>44</sup>

A recent study by Girometti *et al.* (2022) described the demographic and clinical characteristics of 54 confirmed monkeypox cases in the UK in 2022, and found that 9% of cases (n=5) required hospitalization, primarily due to pain or localized cellulitis requiring treatment.<sup>51</sup>

## Asymptomatic Monkeypox Infection

Asymptomatic monkeypox infection is thought to be uncommon, with WHO estimating that 0.1% of cases are asymptomatic.<sup>3</sup> The occurrence of asymptomatic monkeypox has been alluded to by studies that look at immunological responses to *Orthopoxvirus* or monkeypox virus.<sup>72,73</sup> In a targeted literature review on July 1, we found 3 studies that provided immunological evidence consistent with monkeypox infection in people who reported no monkeypox -like symptoms,<sup>57,74,75</sup> as well as 1 study conducted during the 2022 monkeypox multi-country outbreak that provided virological evidence of asymptomatic monkeypox infection.<sup>76</sup> We have since identified 1 additional study.<sup>7</sup>

## Virological Evidence of Asymptomatic Monkeypox Infection

Ferré *et al.* (2022) conducted retrospective testing of all anorectal swabs that were collected for gonorrhoea and chlamydia testing at a French clinic from June 5 to July 11, 2022 and that were found to be negative for both bacteria.<sup>7</sup> As per French screening guidelines, specimens were collected from asymptomatic individuals who self-identified as men who have sex with men (MSM), and who had multiple sexual partners, as part of routine quarterly testing for bacterial sexually transmitted infections.<sup>7</sup> Additionally, all individuals were either taking PrEP for HIV at the time of specimen collection, or were living with HIV and receiving HIV antiretrovirals.<sup>7</sup> Due to laboratory biosafety restrictions, testing for gonorrhoea and chlamydia was not performed when individuals presented with symptoms consistent with monkeypox infection.<sup>7</sup> In total, 213 anal swabs were collected from men who were negative on monkeypox screening (asymptomatic) at the time of specimen collection.<sup>7</sup> PCR testing of 200 anal swabs detected 13 with monkeypox infection (6.5%).<sup>7</sup> Further follow-up with these individuals found that none reported experiencing symptoms of monkeypox, however 2 of the 13 individuals subsequently reported to the clinic with compatible symptoms.<sup>7</sup> One individual had a Ct value of 20.7 while asymptomatic, which increased to 33.0 when symptoms developed a week later. The other individual had an initial Ct value of 38.2 while asymptomatic, which decreased to 24.0 when symptoms developed 9 days later.<sup>7</sup> Of the 187 asymptomatic individuals who initially tested negative for the virus, a further 3 individuals subsequently presented to the clinic with symptoms of monkeypox infection more than 3 weeks later and tested positive.<sup>7</sup>

De Baetselier *et al.* (2022) conducted retrospective screening of 224 specimens collected for gonorrhoea and chlamydia testing. Anorectal swabs, oropharyngeal swabs, and/or first-void urine samples from persons screened for sexually transmitted infections at a Belgium clinic in the month of May 2022 were retrospectively tested by a monkeypox -specific polymerase chain reaction (PCR).<sup>76</sup> Out of 224 specimens, 3 unvaccinated, immunocompetent individuals tested positive for monkeypox, with low anorectal swab Ct values. None of them reported any symptoms in the two months before and three weeks after the sample was taken. None reported exposure to a confirmed monkeypox case, and none of their contacts developed clinical monkeypox. As the Ct values of the specimens from the asymptomatic cases were in the same range as those from symptomatic cases in the clinic (mean = 25.5; SD = 7.9; n = 43), this could suggest possible asymptomatic infection or undetected infection (e.g., unrecognized lesion).

## Immunological Evidence of Asymptomatic Monkeypox Infection

Hammarlund *et al.* conducted a study of twenty Wisconsin residents who had close contact with individuals or prairie dogs infected with monkeypox in the 2003 monkeypox outbreak. Participants were recruited to provide a blood sample for the development of new diagnostic methods for monkeypox.<sup>74</sup> Three study participants (all of whom had a history of previous smallpox vaccine at least 13 years prior to exposure) denied symptomatic monkeypox infection and their blood samples presented immunological evidence of monkeypox infection, including high antibody titers against vaccinia and/or strong antibody titres against monkeypox at 2-4 months post-exposure.<sup>74</sup>

In assessing the human immune responses at 7-14 weeks (convalescence) and at one year post-exposure to animals infected with monkeypox following the 2003 monkeypox outbreak in the U.S., Karem *et al.* (2007) observed anti-orthopoxvirus immune (IgM, IgG, CD4, CD8 and B-cell) responses consistent with infection in contacts who had reported no monkeypox-like symptoms.<sup>75</sup> At convalescence, IgG was detected in 2 unvaccinated children (ages 12 and 13 years) and B-cells were detected in a 42-year old unvaccinated adult, despite non-detection of IgM at both convalescence and 1-year post-exposure.<sup>75</sup> At 1-year post-exposure, IgM was detected in a 60-year old with a remote history of smallpox vaccination, CD8 T-cells were detected in a 56-year old vaccinated individual, and IgG and B-cells were detected in an unvaccinated 35-year old.<sup>75</sup>

## Vaccine Effectiveness

Prior to the global eradication of smallpox and cessation of smallpox vaccination campaigns in 1980 (and earlier in some countries), 1<sup>st</sup> and 2<sup>nd</sup> generation smallpox vaccines were routinely used. These vaccines were found to be effective in preventing smallpox infection in 85-95% of vaccinated individuals, with protection lasting for several years.<sup>77</sup> Individuals who previously received smallpox vaccine may have some (likely waning) cross-protective immunity to monkeypox virus, and if infected with monkeypox virus, may experience milder illness compared to those who have never received smallpox vaccine.<sup>77</sup>

Imvamune<sup>®</sup> vaccine is a licensed 3<sup>rd</sup> generation smallpox vaccine that provides active immunization against *Orthopoxvirus* infection (including monkeypox) and is authorized for use in Canada in adults aged 18 years or older. Although Imvamune<sup>®</sup> is authorized as a 2-dose primary series, in Ontario and elsewhere it is being deployed primarily as a single-dose for post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) to maximize the number of people at high risk of exposure to the virus who can be protected.<sup>32</sup>

There is currently minimal published literature assessing the effectiveness of 1-dose PrEP or PEP. Prior to the current global monkeypox outbreak, the UK has previously provided Imvamune<sup>®</sup> to young children, including infants, as PEP as part of their incident response to imported cases of the virus.<sup>78</sup> No known adverse effects were noted following vaccine administration to children.<sup>78</sup>

Thy *et al.* (2022) examined cases occurring after receipt of a single dose of smallpox (Imvanex<sup>®</sup>, also known as Imvamune<sup>®</sup>) vaccine given as PEP to 276 high risk contacts in France.<sup>79</sup> Exposures deemed to be high risk included close skin-to-skin or mucosal contact with an individual with confirmed monkeypox infection (based on the outcome of PCR testing), indirect contact with a contaminated textile or surface, or prolonged ( $\geq 3$  hours) close ( $< 2$ m) contact with an infected individual.<sup>79</sup> Cases were predominantly male (90.6%) with a median age of 19 years (IQR: 14-25 years).<sup>79</sup> Most individuals self-identified as gbMSM (88.3%). All 276 individuals received PEP within a median of 11 days following exposure (IQR: 8-14 days).<sup>79</sup> Twelve individuals subsequently developed monkeypox infection; ten individuals developed infection within 5 days of receiving PEP, and 2 individuals developed a breakthrough infection, with



onset of signs and symptoms at 22 and 25 days post-PEP.<sup>79</sup> The authors concluded that while the vaccine was generally effective in preventing monkeypox infection in 96% of individuals who had sustained a high risk exposure to the virus, the vaccine did not fully prevent infections.<sup>79</sup> The authors further noted that individuals who experienced an infection following vaccination appeared to have mild, uncomplicated illness; however, results are to be interpreted with caution due to small sample size and as the study was observational in design.<sup>79</sup>

Various jurisdictions are undertaking studies to explore the effectiveness of the smallpox vaccines being used to prevent monkeypox infection during the current global outbreak.<sup>71</sup> The outcome of this research is anticipated to inform recommendations on the need for additional booster doses of vaccine for individuals deemed at ongoing risk of non-occupational exposure to the virus.<sup>71</sup>

## Length of Immunity

Limited research on the duration of immunity following natural infection with monkeypox virus appear to show that there may be some protective immunity for at least a year following infection with the virus.

A study by Karem *et al.*, (2007) assessed monkeypox immunity following the 2003 monkeypox outbreak in Wisconsin.<sup>75</sup> The study included data from 72 participants; 27 were designated as cases and 45 were designated as contacts.<sup>75</sup> The participants were further categorized into four groups based on history of receiving an earlier generation smallpox vaccine and case status (case or contact): cases with previous smallpox vaccination (n=6), cases without previous smallpox vaccination (n=21), contacts with previous smallpox vaccination (n=27) and contacts without previous smallpox vaccination (n=18).<sup>75</sup> Orthopox-specific IgG, IgM, CD4 and CD8 T-cell and B-cell responses were measured and compared at 7-14 weeks (convalescent period) and again at 1-year postexposure.<sup>75</sup>

- IgM responses were maintained in both vaccinated (1 of 5) and unvaccinated (5 of 11) monkeypox cases following 1 year post-rash onset.<sup>75</sup>
- IgG levels were observed in all cases (16 of 16; 5 vaccinated cases and 11 unvaccinated cases) 1 year post-rash onset.<sup>75</sup> Both vaccinated and unvaccinated individuals demonstrated a decline in IgG levels from convalescent to 1-year memory sampling at ~20% for vaccinated individuals and ~40% for unvaccinated individuals.<sup>75</sup> In contrast, the majority of contacts, regardless of vaccination status, demonstrated no change in titer from convalescent to 1-year memory sampling.<sup>75</sup>
- Orthopox-specific CD4 T-cell reactivity was observed in 5/5 vaccinated and 6/7 unvaccinated cases with similar geometric mean levels at convalescence and at 1 year post-rash onset.<sup>75</sup>
- Vaccinated cases (5 of 5) and unvaccinated cases (7 of 7) had detectable orthopox-specific CD8 T-cell reactivity at 1 year post-rash onset, with higher geometric mean levels in unvaccinated cases.<sup>75</sup>
- Memory B-cells were detected in 5 of 5 vaccinated cases and 8 of 8 unvaccinated cases at 1 year post-rash onset.<sup>75</sup> Among vaccinated cases, 3 had decreased orthopox-specific B-cell counts while 1 had increased counts at 1 year post-rash onset.<sup>75</sup> Among unvaccinated cases, orthopox-specific B-cell counts remained similar from convalescence to 1 year.<sup>75</sup>

- The authors noted that immune response appeared to differ depending on the severity of disease (categorized based on the number of lesions), although observed differences were not significant.<sup>75</sup>

A study by Sivapalasingam *et al.* (2007) compared immunity (both cellular and humoral) to vaccinia virus (VV) in individuals who had previously been exposed to an orthopoxvirus, including seven cases from the 2003 monkeypox outbreak in Wisconsin (2 of which had a history of receiving a VV containing vaccination).<sup>80</sup>

- 1 year after monkeypox virus infection, 7 of 7 individuals had VV-specific lymphoproliferative responses; 6 of 7 had detectable IFN- $\gamma$  ELISPOT responses, 2 of 7 subjects had cytotoxic T lymphocyte responses, and 3 of 7 had a VV-specific neutralizing-antibody titer  $\geq 1:20$ .<sup>80</sup>
- Two VV vaccine-naïve individuals who had a positive response for all 3 cellular immune response assays did not have detectable serum neutralizing antibody to VV.<sup>80</sup>
- The authors noted that their findings may indicate cross-protective immunity between VV and monkeypox virus.<sup>80</sup>

## Diagnostic Assays

As of June 23, 2022, all specimens submitted to the Public Health Ontario Laboratory for monkeypox testing are tested using a multiplex PCR assay that detects two targets:<sup>81</sup>

- A generic monkeypox virus target that detects both Clade I and Clade II of the virus, and
- A target that only detects Clade II of the virus.

Specimens with low level (cycle threshold (Ct)  $\geq 35$ ) or indeterminate (Ct 38.01-39.99) result(s) in one or both monkeypox virus targets may undergo further review and investigation.<sup>81</sup> This scenario may occur due to low viral target quantity in the specimen approaching the assay's limit of detection, or due to nonspecific reactivity (a false signal) in the specimen. Testing by *Orthopoxvirus* PCR and evaluation of *Orthopoxvirus* target gene Ct, together with epidemiological risk factors and clinical presentation, is required for final interpretation.<sup>81</sup> Specimens from pediatric (<18 years) and female patients in which either or both monkeypox virus targets is detected, or for which an indeterminate result is received, will undergo further testing by *Orthopoxvirus* PCR or gene sequencing to confirm whether monkeypox virus is present.

Minhaj *et al.* (2022) noted the potential for false positive results to occur, following the identification of 3 individuals in the US who were given a diagnosis of monkeypox infection and subsequently found to have a false-positive test result.<sup>82</sup> All 3 individuals presented with atypical signs of monkeypox infection, and had no known exposures to the virus or risk factors for infection.<sup>82</sup> Two of the individuals were children, and 1 individual was a pregnant woman.<sup>82</sup> False positive test results may occasionally occur due to laboratory cross-contamination and high test sensitivity.<sup>82</sup> The authors recommended that in the event of a positive monkeypox test result (Ct  $\geq 34$ ) in an individual without a high pre-test probability of infection (i.e., atypical symptoms, no known risk factors for infection, or no epi-link to a confirmed case), specimens should be re-extracted and re-tested in order to avoid unnecessary public health intervention.<sup>82</sup>

# Ontario Risk Assessment

WHO currently considers the global risk of monkeypox virus transmission to be moderate, with varying risks at the regional level.<sup>2</sup> Based on current epidemiological information and the capacity of individual countries to detect and respond to cases of infection, WHO and PAHO have assessed the overall risk of transmission at the regional level in the Americas to be high (September 13, 2022).<sup>83</sup> This assessment by WHO and PAHO is based on consideration of local epidemiology, the risk of case importation, and local capacity for outbreak detection and response.<sup>2</sup>

Currently the risk of monkeypox virus transmission to the general public in Ontario is considered low with a low degree of uncertainty. The risk of monkeypox causing severe disease or impacting diagnostic testing in Ontario is low with a low degree of uncertainty. The risk of reinfection is low with a low degree of uncertainty. The risk of monkeypox infection after receiving PrEP (14 or more days after administration) or PEP (within 14 days of a known exposure) is low with a moderate degree of uncertainty. The overall risk assessment for monkeypox may change as new evidence emerges (see Table 1).

Given the current epidemiology in Ontario, the risk of monkeypox virus transmission among the gbMSM community in Ontario is considered to be within a continuum from low to moderate with moderate uncertainty. Risk factors including sex with multiple partners and anonymous sex as well as Imvamune<sup>®</sup> vaccine uptake at the individual and population level will influence the risk of individuals who identify as gbMSM risk acquiring monkeypox virus infection.

**Table 1: Risk Assessment for monkeypox in Ontario**

Issue	Risk Level	Degree of Uncertainty
Increased Transmission	Low (general population)	Low
	Low to moderate* (gbMSM community)	Moderate
Severe Disease	Low	Low
Reinfection	Low	Low
Monkeypox infection 14 or more days after receiving PrEP	Low	Moderate
Monkeypox infection within 14 days of receiving PEP following a known exposure	Low	Moderate
Impact on Diagnostic Testing	Low	Low

\*Risk is on a continuum from low to moderate based on risk of exposure

## Implications for Practice

Physicians and healthcare providers/professionals providing health care, particularly to patients who identify as gbMSM, should be aware of the current status of monkeypox transmission in the community. Recognition of potential cases of monkeypox infection will enable implementation of appropriate prevention and control measures.

Public health surveillance efforts should continue to monitor for changes to monkeypox epidemiology and known risk factors including transmission to other populations in order to review and update vaccine eligibility criteria as required.

Public health surveillance, contact tracing, and outbreak prevention and control measures should be maintained, even if the incidence of new cases appear to be declining. Early removal of outbreak prevention and control measures may lead to a resurgence in cases and successive waves of infection, particularly given the potential for undetected cases and transmission to be occurring within the community. In addition, a return to normal sexual behaviours amongst the affected population combined with an unknown efficacy of a single dose of PrEP, could lead to an increase in cases in the coming months and should be monitored closely. Further, receipt of a complete primary series of Imvamune® vaccine for eligible individuals is expected to further reduce the risk of ongoing transmission amongst the affected population.

Public health authorities should continue to review scientific evidence (e.g. routes of transmission, disease severity, etc.) as well as case and contact management guidance from other jurisdictions in order to inform the public health response in Ontario.

A non-stigmatizing and community engagement approach to risk communication is key to removing barriers to healthcare seeking behaviour, including accessing PrEP monkeypox vaccine for those at risk of exposure to the virus. Strategies shown to be successful in promoting community engagement and vaccine uptake should be considered in communities experiencing increased transmission of the virus. It is important to note that while the risk of monkeypox virus transmission is currently increased in the gbMSM community due to currently observed transmission patterns, all individuals are susceptible to the virus, regardless of gender or sexual orientation.

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## Specifications and Limitations of Evidence Brief

The purpose of this Evidence Brief is to investigate a research question in a timely manner to help inform decision making. The Evidence Brief presents key findings, based on a systematic search of the best available evidence near the time of publication, as well as systematic screening and extraction of the data from that evidence. It does not report the same level of detail as a full systematic review. Every attempt has been made to incorporate the highest level of evidence on the topic. There may be relevant individual studies that are not included; however, it is important to consider at the time of use of this brief whether individual studies would alter the conclusions drawn from the document.

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