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Review

Monkeypox and its Possible Sexual Transmission: Where are we now with its evidence?

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Abstract

Monkeypox is a rare disease which is rising nowadays in different countries since the first case in the UK was diagnosed on May 6, 2022, by the United Kingdom (UK) Health Security Agency. Then more than 12,500 cases were identified in over 68 countries up to July 18, 2022. In endemic areas, the monkeypox virus (MPXV) is commonly transmitted through zoonosis, while in non-endemic regions, it is spread through human-to-human transmission. Symptoms can include flu-like symptoms, rash, or sores in hands, feet, genitalia, or anus. In addition, people who did not take the smallpox vaccine were more liable to be affected than others. The exact pathogenesis and mechanisms are still unclear; however, most identified cases are reported in men who have sex with other men (MSM). According to the CDC, transmission can happen with any sexual or non-sexual contact with the infected person. However, a recent pooled meta-analysis reported that sexual contact is involved in more than 91% of the cases. Also, it is the first time that semen analysis for many patients has shown positive monkeypox virus DNA. Therefore, in this review, we will describe transmission methods for MPXV while focusing mainly on potential sexual transmission and associated sexually transmitted infections. We will also highlight the preventive measures that can limit the spread of the diseases in this regard.

Keywords: sexual transmission; monkeypox; emerging; global; epidemic.

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1. The Epidemiology of Monkeypox

In 1958, the Danish virologist Preben Christian Alexander von Magnus discovered the monkeypox virus (MPXV) in Copenhagen [1]. It was reported as a zoonotic disease transmitted from animals to humans by MPXV. It is a double-stranded DNA virus belonging to the Orthopox genus of the Poxviridae family. The Orthopox genus also includes cowpox, smallpox, and rabbitpox. Monkeypox (MPX) was first reported in Monkeys, although it is believed that Rodents are the natural host [2]. The smallpox vaccine protected MPX as they are genetically closely related. There are two types of MPXV, the Central African (Democratic Republic of Congo) clade and the West African clade (now called clades 1 and 2, mainly), with the first having a 3.6% and the latter with a 10.6% fatality rate [1, 2]. MPX is transmitted zoonotically by direct contact with body fluids, blood, or lesions on infected animals and therefore was reported as an occupational disease [2]. It was listed by the World Health Organization (WHO) as having epidemic and pandemic potential [3].

The first case of human infection was reported on September 1 1970. A 9-month-old child was admitted to a Democratic Republic of Congo hospital. He presented with a fever and rash that had developed two days prior; upon examination, hemorrhagic lesions with centrifugal distribution were noted [4]. The patient was suspected of having smallpox, but genome sequences confirmed the presence of both the West and Central African clades of MPXV [5]. MPX has since spread to several African countries and remained endemic in Central and West Africa, including countries such as the Democratic Republic of Congo (DRC), Central African Republic, Nigeria, and Liberia, among others [5].

Human-to-human transmission emerged after the 1996-1997 Democratic Republic of Congo outbreak [6]. The transmission was reported caused by direct contact with rash, scabs, sores, scabs or contaminated objects or an infected person, and respiratory droplets [2]. The CDC reported that transmission might also occur by hugging, kissing, contact with the anus or genitals of an infected person, and oral, anal, and vaginal sex [7]. It was also linked to the discontinuation of the smallpox vaccine, weakened immunity and poor living standards [6]. The smallpox vaccine was shown to be 85% effective in preventing MPX. It has an incubation period ranging from 5-21 days with a similar clinical presentation to that of smallpox [5].

The current outbreak was confirmed in early May 2022, with several cases reported in Spain, Portugal, the UK, and the Americas. There are no obvious epidemiological links between the cases, and it is yet to be identified. However, the geographical dispersal is much greater than in past outbreaks. During the first week of the epidemic, suspected and confirmed cases were reported in 24 countries, some of which had travel links to Europe [8]. There were 920 confirmed and 70 suspected cases, and within a month, the numbers have increased by over ten folds, leading to a total number of confirmed cases of 12608 in 66 countries, as of July 16, 2022 [9]. It is evident from available data that more than 50% of confirmed and suspected cases are in European countries. Spain reported 2835 confirmed cases, the highest in any country to date, followed by Germany with 1859 confirmed cases, the United States (US) with 1813 confirmed cases, the UK with 1778 confirmed cases, and France with 908 cases and the Netherlands with 549 confirmed cases. In addition, countries including India, New Zealand, Georgia, Ecuador, Lebanon, Russia, Saudi Arabia, South Korea, and Turkey have reported one confirmed case of MPX.

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2. Diagnosis and Clinical Presentation of Monkeypox

Suspected cases are defined as a (1) person with sudden symptom onset of rash with or without anogenital complaint unexplained by other differential diagnosis and (2) one or more of the following: fever of sudden onset, myalgia, headache, backache, asthenia, or lymphadenopathy [10]. A probable case is reported as one that meets the suspected criteria and has demonstrated the presence of MPXV by PCR, immunohistochemical test, electron microscopy, or has detectable levels of IgM antibodies within 4-56 days after rash presentation. A confirmed case is a laboratory-confirmed infection; PCR confirmed MPXV or culture confirms the presence of MPXV isolated from a skin lesion. Cases are excluded from the above classification if they do not develop a rash within five days, absence of MPXV in the specimen, absence of antibodies, or if a differential diagnosis is confirmed [11].

The US CDC reported that MPX infection has an incubation period of 1-2 weeks before the appearance of initial symptoms, with infection usually lasting 2-4 weeks. The severity of infection depends on the patient's prior health, mode of infection, and the strain of the virus. The Central African clade has shown more severe signs and symptoms with a higher mortality rate when compared to the West African clade [12].

Clinical manifestations of MPX are grouped into invasion and skin manifestation periods. Invasion periods include flu-like symptoms such as headaches, fever, malaise, chills, and lymphadenopathy during the prodromal period. Skin manifestations are non-pleomorphic and observed 1-3 days later, appearing in the sequential stages of macules, papules, vesicles, pustules, crust, and scars. Skin lesions are typically painful and last 2-4 weeks before completely healing and falling off [2]. MPX rash is mainly presented as vesicles or pustules that are firm, deep seated, well circumscribed, and often develop umbilically. These lesions are contagious from their onset till the formation of a scab and are commonly confused for chickenpox or smallpox [11]. Skin pigmentation and scars may remain.

The most common signs and symptoms include fever (reported in 54.29% of cases), inguinal lymphadenopathy (45.71%), exanthema (40%), ulcers and vesicles on the genitals and anal region (31.43%), asthenia and fatigue (22.86%), headache (25.71%), myalgia (17.14%), cervical lymphadenopathy (11.43%), and axillary lymphadenopathy (5.71%) [1]. Some patients reported having a rash followed by other symptoms, while others only reported a rash without prodromal symptoms followed by systemic symptoms/signs [7]. Patients present with fever before the rash, and lymphadenopathy presents with the onset of fever or rash or 1-2 days after the beginning of rash.

Typically, the rash first appears on the face and then spreads to other areas of the body; however, many studies reported an atypical presentation, with the most common initial manifestation being on the perianal or genital region, followed by a monomorphic and centrifugal distribution [1, 11]. According to the data from reported cases in the US, it was reported that the most common site for the rash throughout the time of infection is the arm, trunk, leg, face, hand, perianal, oral, neck, genital, and feet in order of most common to least common [11]. It has been suggested that the presence of herald lesions at the point of sexual contact and the absence of prodromal symptoms suggest sexual transmission [13]. One Australian case reported a superinfection presenting bacterial cellulitis of the penile shaft and lower central abdomen [1].

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3. Transmission Methods of Monkeypox Virus

3.1. Non-sexual transmission

MPX disease could be transmitted either from zoonosis or through human-to-human transmission. From 1970 to 2003, the endemic areas for MPX were the rainforest of Africa [14]. While in 2003, the outbreak of MPX was first identified outside the endemic regions in Africa and appeared in the US. Since then, sporadic outbreaks have spread worldwide, all linked to travel to endemic areas in Africa [14]. Since MPXV belongs to orthopoxviruses, it could be transmitted through zoonosis. The same animal reservoir is still unclear; since monkeys were eliminated as candidates as they are the natural reservoir for the virus [14]. Gambian marsupial, tree squirrel, and rope squirrel could be potential reservoirs for the MPXV [10, 14]. MPX disease is common among rodents in Africa as well [10]. Transmission could be through direct contact with body fluid or blood or MPX lesions of infected animals. Moreover, inadequately cooked meat could transport the disease [2].

According to the CDC, an individual can get infected with the MPXV in different ways related to sexual or non-sexual contact. For non-sexual contact, it could be transmitted in different ways. First, direct contact with MPX rash, sores, or scabs. Second, contact with objects and surfaces that someone with MPX uses. Third, respiratory droplets or oral fluids from a person with MPX. In the new outbreak of 2022, the first case reported in the UK reported a history of travelling to endemic areas (Nigeria). Also, in Portuguese, three patients had contact with animals (two patients with cats and one with pigs), and another reported contact with another patient [1]. However, there isn't any epidemiological link between a large number of cases of MPXV and central or western Africa [14, 15]. That may indicate that MPXV spread among people for a prolonged period through human-to-human transmission without detection [15]. That being said, MPX was also identified to transport from human to human such as in household contacts and shared housing inhabitants (e.g., in prisons), and health care providers who had direct close and sustained contact with patients of MPXV [11].

3.2. Potential Sexual transmission

Even though it is widely known that most at-risk of MPXV transmission are people with a history of close physical contact with a symptomatic person, evidence has shown another appealing way of possible transmission. Available data indicate that MPXV cumulative cases have mostly been documented amongst men who have sex with men (MSM) [7]. Sexual contact or multiple or different sexual partners in the 21 days before symptom onset has been described as one of the risk factors by the WHO. That brings curiosity regarding a possible sexual transmission. For instance, 54 cases presented at one health centre in the UK were all documented amongst MSM [16]. That was similar in Italy, where four documented MSM-MPX cases reported having sexual intercourse without using a condom [17]. Sexual contact could be the most important risk factor for MPXV in specific populations, particularly among MSM, resulting in a staggering number in line with this category. A recent review showed that "sexual exposure" could be reported in 91.67% of the cases (n=124) [1]. That was prominent, although preliminary, particularly in unprotected sexual intercourse with multiple partners, random or anonymous, respectively [1]. Such a rate is significant and points out that despite being less documented, sexual intercourse could be an important route of disease transmission. However, it should be confirmed in further studies, not only epidemiological but especially

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in assessing viral infectivity and replication in cell cultures, using isolated viruses from seminal or sexual fluid samples.

In addition to existing symptoms of MPXV, the recently documented manifestations of the disease are signs of sexual transmission mode. Some lesions were found on the genital organ, such as deep-seated and well-circumscribed lesions [17]. Other perianal lesions include itching papules and inguinal lymphadenopathy. Interestingly, the Samples obtained from genital and anal lesions had similar results as samples collected from the skin, faeces, seminal fluid, nasopharynx, serum and plasma in MPXV DNA in real-time PCR. MSM was the most commonly identified population to be much more affected by MPXV. That is supported by the recent evidence highlighting that more than 80% of cases were either gay or bisexual [18].

Another vital point to consider is the coinfection of MPXV and other sexually transmitted infections (STIs). The cases identified in this community of concern were found in MSM who had been diagnosed with STIs. For instance, all MSN diagnosed with MPXV had previous STIs, Hepatitis C, Syphilis and human immune-deficiency virus (HIV) [17]. The association between MPX and HIV has been documented in endemic zones. For example, a study conducted in Nigeria found a correlation between HIV patients with MPXV [19]. This study revealed that coinfection of HIV type 1 and MPXV had larger lesions in the skin and genital ulcers than negative HIV cases. Interestingly, the recent CDC (USA) results reported a possible coinfection of MPXV and STIs. Like elsewhere during the current outbreak, there were patients with MPX who also had chlamydia, herpes syphilis, and gonorrhoea infections [20].

As mentioned above, MPXV would be transmitted sexually. That is supported by laboratory analysis that found positive MPXV qPCR in the seminal fluid of MSM in Germany and other countries [21]. Similarly, a study conducted in Italy has supported a possible association between MPXV and sexual transmission. The INMI Monkeypox group showed that clinical features, including anal and genital lesions, were the first to appear among MSM, whose semen analysis showed MPXV DNA [17].

Furthermore, data from London, UK, reports favour sexual contact transmission as 54 participants, all MSM, tested positive for the MPXV test. Moreover, they presented clinical characteristics, including genital and perianal lesions and appealing sexual transmission [16]. Therefore, given the population of interest, their clinical features and the laboratory results, there is a possible link between MPXV and sexual transmission, thus speculating MPXV is a sexually transmitted infection (STI) despite the paucity of data to document it. Therefore, there is a need for global research to establish the possibility of this unusual sex transmission route among MPXV patients, particularly MSM.

4. Transmission-related Preventive Measures

Health experts usually recommend various approaches to contain the dissemination of an outbreak, especially ones that affect worldwide thousands of individuals and communities and cause serious health issues to the affected patients. In this context, various approaches have been proposed to limit MPV transmission and reduce the number of affected patients. These include isolation approaches (aiming at decreasing the risk of animal-to-human and human-human-to-human transmission), vaccination, and educational programs that aim to enhance individual-based awareness about the best practices to intervene against MPV infection. We will shed more light on these approaches in the following sections.

4.1. Reducing Transmission

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During outbreaks, healthcare authorities must seek the identification and provide surveillance of new cases. In addition, evidence indicates that a remarkable risk factor to consider during MPV outbreaks is close contact with infected MPX cases. Therefore, healthcare experts have provided different prevention approaches that the public should commit, including 1- isolation of infected patients from healthy individuals, 2- using disinfectants that are Environmental Protection Agency–registered, and 3- using appropriate personal protective equipment and practising good personal hygiene to provide the best intervention, especially for household members that are in direct contact with infected cases [11].

Besides, household members and healthcare workers (HCWs) having direct or close contact with infected cases have the highest risk of infection. Therefore, frontline HCWs (usually in direct contact with suspected and confirmed MPX patients or others checking them for specimens) and household members must commit to standard infection control measurements. Besides, it can be suggested that individuals previously vaccinated against smallpox should be selected to deal with the current cases. Moreover, isolation and screening of individuals travelling from endemic communities are essential. Accordingly, some evidence suggests that such individuals and suspected cases should be quarantined for three weeks [2]. However, no clear guidelines were provided in the literature in this context.

Evidence shows that animal-to-human transmission has been responsible for many cases of MPV infections. Therefore, direct contact with wild confirmed/suspected cases of animals should be prohibited. Avoiding contact with blood, meat, or other body parts, whether the animal is dead or alive, is encouraged. Besides, animal meat should be adequately cooked before eating. Restricting international animal trading should also be adopted, especially in countries that import animals from endemic areas. That should include non-human primates and rodents.

Moreover, isolation of infected animals is encouraged to prevent transmitting the infection to other animals and humans. A 30-day quarantine should also be provided for animals having close contact with other confirmed animal/human cases. These animals should be handled according to standardised infection control measures, and symptoms should be observed through the isolation period [7]. Finally, further studies are encouraged to outline the reasons behind the outbreaks in non-endemic areas. That should be directed to investigate the potential sources of infection and reduce the intensity and spread of the disease.

4.2. Vaccination

No vaccines have been developed for MPV infection. However, past evidence indicates that smallpox vaccines can prevent the spreading MPV infections due to cross-reaction, with an estimated efficacy of 85% [12]. Accordingly, two smallpox vaccines have been approved for preventing MPV, including the second-generation smallpox vaccine ACAM2000, approved by the Food and Drug Administration for post-exposure prophylaxis, and the third-generation JYNNEOS™, approved for different population groups.

Various investigations indicated the efficacy of these vaccines [21-28]. However, the central dilemma in using them lies within their associated adverse events. For instance, some studies reported that ACAM2000 should not be given to patients with atopic dermatitis and those with vulnerable immune systems (including patients with recent stem cell transplantations and others with immunocompromising conditions or receiving immunosuppressants) [28-31]. On the other hand, JYNNEOS™ has an enhanced safety profile. It is a non-replicating vaccine with low immunological reactogenicity to different generations of smallpox vaccines, with its proven efficacy in animal and human studies [31-36].

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Moreover, the response of public health authorities is essential to help contain such outbreaks. For instance, the CDC has provided the availability of post-exposure prophylaxis vaccines for contacts with intermediate (after contacting an unmasked patient for ≥3 hours within ≤6 ft without wearing a mask) and high-risk exposures. On the other hand, post-exposure prophylaxis should not be given to individuals with uncertain or low-risk profiles (like HCWs contacting a patient without eye protection) [37].

Applying ring vaccination is also encouraged. The approach was successfully used in previous outbreaks, including smallpox and Ebola virus outbreaks [38-40]. It is done by vaccinating family members/households and members with the parameters of a confirmed case. Besides, the strategy should include contacts and contacts of contacts to infected patients, irrespective of their geographical distribution. This might not be easy to apply, and providing vaccines might not be feasible for these individuals. Therefore, contact tracing through a systematic approach, early identification and isolation of cases, and strict application of other prevention approaches are essential, especially when vaccines cannot be offered. These measurements are also encouraged due to the stoppage of smallpox vaccination [41, 42]. This poses an additional challenge for healthcare authorities to deliver vaccines on a wide scale and enhance the attitudes of populations refusing vaccination [43-45].

4.3. Others

Raising awareness of the general public and individuals having close contact with MPV cases is also essential to enhance prevention and reduce transmission of MPV. Accordingly, different educational campaigns can be provided. For instance, training healthcare individuals responsible for dealing with confirmed/suspected cases and others accountable for collecting specimens is mandatory. Furthermore, safe storage, handling, and transportation of human/animal specimens should be done with triple packaging according to the WHO guidance for transporting infectious substances [46]. Moreover, enhancing the knowledge (about the symptoms, signs, transmission, and prevention) and attitude (towards sticking to the different prevention approaches and seeking medical care whenever needed) among the public and highly-vulnerable groups should be provided.

It is essential to consider the stigma caused by the increasing pressure, especially on the LGBTQI+ minty, secondary to the growing claims that many confirmed MPV cases are individuals that identify themselves as "men who have sex with men" [6]. However, as we mentioned in an earlier section, sexual transmission is not the only route of transmitting the infection. Furthermore, close physical contact (including sexual transmission) is not limited to these communities, irrespective of gender identity and sexual orientation. Therefore, although sexual transmission is a significant route for transmitting the infection, it should not be specified as the only route, similar to what happened in the eighties during the HIV outbreaks [47, 48], which was associated with severe healthcare concerns and worsened the situation. Therefore, public and healthcare authorities should provide measures to overcome this stigma.

Accordingly, public communications should indicate that the disease is not limited to specific communities and is a global public health concern that requires the integration of the public and commitment to the different prevention approaches, rather than generating a gender-based stigma, which can only make matters worse [49]. On the other hand, it is also practical not to neglect educational campaigns for these groups, which should also increase their awareness and attitude towards the infection. For instance, educational campaigns should be directed to seeking and following healthcare experts' prevention and

treatment recommendations. Moreover, avoiding sexual intercourse and being in close contact with confirmed/suspected cases should be prioritised [7].

5. Conclusions

MPXV is now widely spread in Europe and different countries across the world. It has different modes of transmission. Sexual contact is considered an important mode of transmission. Men who have sex with other men are more liable to get infections than others. Recent evidence also highlights an association between MPX and STIs such as HIV, which warrants further investigations to assess the disease's burden carefully.

Furthermore, efforts should be directed towards limiting the spread of the diseases, not just by case tracking, isolation, and vaccination, but also through controlling the contributing factors to disease transmission, either sexually or non-sexually. This can be tackled by providing educational programs for the public regarding transmission methods, limiting the stigma associated with identifying sexually transmitted cases and providing proper management for such cases. Finally, we are on the verge of an MPX pandemic. Therefore, all efforts and available resources should be directed towards investigating this disease and its preventive measures to contain it before it affects millions, as COVID-19 did.

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