MONKEYPOX

A neglected infection becomes re-emerging global challenge

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Monkeypox (MPX) was first discovered in 1958 when two outbreaks of a pox-like disease occurred in colonies of monkeys kept for research. Despite being named "monkeypox", the source of the disease is still unknown. However, African rodents and some primates may harbor the virus and infect people. In humans, the first case was described in 1970 in a 9-year-old child in the Democratic Republic of the Congo (DRC), nine months after the eradication of smallpox in that country. This was followed by sporadic cases reported from the rainforest areas of central and western Africa. The outbreaks were enrolled mainly in the DRC, where the disease is currently considered endemic. Outside Africa, the first MPX outbreak with 81 human cases was reported in the United States (US) in 2003 after close contact with predominantly prairie dogs. In September 2018, three individual patients in the United Kingdom (UK) were diagnosed with MPX; two had recently travelled to Nigeria, and the third case was a healthcare worker caring for one of the cases. In 2018-2019 in Israel, Singapore and UK the sporadic cases of imported MPX from Nigeria reported [1,2].

In May 2022, a family cluster of two non-travel related cases and several cases in men who have sex with men (MSM) were registered in the UK. Subsequently, the same situation was reported in Portugal, Spain, Belgium, Germany, France, Italy, Sweden, Switzerland, the Netherlands, Austria, Slovenia, Finland, Malta, Norway, Hungary, Canada, the US, Australia, Israel, the United Arab Emir-

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ates etc., with the latest update also in Georgia and Turkey [1-3].

The causative agent is the monkeypox virus (MPXV), which belongs to the genus Ortho-poxvirus, family Poxviridae [1,2,4]. The Orthopoxvirus genus also includes variola virus (etiological agent of smallpox), vaccinia virus (used in the smallpox vaccine), and cowpox virus. At the same time, despite similarities of the clinical course of the disease, MPX is not related to chickenpox (the causative agent is varicella zoster virus) [1,2].

Poxviruses show extraordinary resistance to drying [5], and increased temperature and pH tolerance when compared with other enveloped viruses. Despite these characteristics, poxviruses are sensitive to common disinfectants, although they can be less sensitive to organic disinfectants compared to other enveloped viruses [1].

MPXV is not considered a biological agent of concern for biosecurity according to the US Centers for Disease Control and Prevention's (CDC) list of bioterrorism agents [6], but it is considered an 'agent with high threat for deliberate release' using the matrix developed by the European Union (EU) task force on Bioterrorism (BICHAT) [1].

Two phylogenetically distinct clades of MPXV have been identified through genomic sequencing: the Central African (Congo Basin) clade (CAC) and the West African clade (WAC). Since 2016, confirmed MPX cases have been reported from the following African countries: Cameroon (WAC), Central African Republic (CAC), the DRC (CAC), Liberia (WAC), Nigeria (WAC), the Republic of the Congo (CAC) and Sierra Leone (WAC). Genetic differences between the viral genomes of the two clades might explain differences in viral clearance and pathogenesis [1]. Typically, the CAC MPXV is associated with more severe disease, higher mortality, and more frequent human-to-human transmission [4,7].

Human-to-human transmission of MPXV was considered to mostly occur through respiratory droplets during close and prolonged face-to-face contact, by direct contact with body fluids of an infected person, or contact with contaminated objects, such as bedding or clothing [2,3,8]. Previously, small clusters in Nigeria among heterosexual partners indicate that transmission through sexual contact is a plausible route of transmission. Other rare transmission routes, such as mother-to-child transmission [14] or nosocomial infection [15,16] have been documented. Based on outbreak data in May 2022, when most cases were found among MSM, sexual transmission is hypothesized to be the main driver of ongoing outbreaks. It is unknown whether and how the risk of transmission varies with the type of sexual contact and exposure (e.g. non-penetrative, penetrative vaginal, penetrative anal, use of preservatives) [1].

Difference in country-by-country approaches concerning case definitions, detection, testing, and reporting strategies affect the actual number of infected individuals, with varying underestimates of the true number of cases and deaths. According to the World Health Organization (WHO) strategy through International Health Regulations (2005) communications, countries should notify only probable and confirmed cases. At the same time, all suspected cases are required to be reported to national authorities [3]. Existing data from polymerase chain reaction (PCR) assays and genome sequencing indicate that the MPXV genomes belong to the West African clade [2].

On 8 August 2022, the WHO released an updated report on the multi-country outbreak of MPX. From 1 January through 7 August 2022, 27814 laboratory-confirmed cases of MPX and 11 deaths have been reported to WHO from 89 countries/territories/areas in all six WHO Regions. The majority of cases reported in the past four weeks were notified from the WHO European region (53%) followed by the Region of the Americas (46%). Since the last edition of this report published on 25 July 2022, 11798 new cases (74% increase), and 14 new countries have reported cases. Six new deaths have been reported. In the contrary to the July of 2022, then three deaths have been reported in Africa, for the first time MPX deaths have been reported in countries outside of the Africa in Spain (two deaths), Brazil (one death), and India (one death). In two cases, deaths have been linked to viral encephalitis and some patients had underlying immune compromising conditions [17].

Besides, a group of global experts convened by WHO has agreed on new names for MPXV variants, as part of ongoing efforts to align the names of the monkeypox disease, virus and variants – or clades – with current best practices. The global health agency labeled Monkeypox variations as Clades I, IIa and IIb. The Congo Basin and West African variants were reclassified as Clade I and Clade II, the latter of which has two subclades [17].

According to the last report (16 August 2022) from European Center for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe, already 19429 cases of MPX have been identified through International Health Regulations

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(IHR) mechanisms from 43 countries the European region. A total of 18960 cases were reported in the European Surveillance System (TESSy) from 36 countries, among them 18847 cases were laboratory-confirmed. Vast majority of cases were reported in male (98.9%). Among cases with known HIV status, 38% were HIV-positive. The commonest symptom was rash (77.1%) and systemic symptoms such as fever, fatigue, muscle pain, vomiting, diarrhea, chills, sore throat or headache (65%). Only 5.8% of patients were hospitalized. 1.7% of cases were reported in Health Care Workers (HCW); importantly no occupational exposure has been reported. The earliest known case by retrospective analyses of a residual sample was identified on 07 March 2022 and the earliest date of symptomatic disease was reported as 03 April 2022. Summary of reported sexual orientations according to TESSy data is as follows: 49.5% self-identified as MSM, 0.5% Bisexual, 0.9% Heterosexual [18].

The current outbreak of MPX is also characterized by atypical clinical manifestations. Previously described classical clinical presentation of MPX, such as fever, swollen lymph nodes, followed by centrifugal rash, is not common for the 2022 outbreak. Typically, the majority of human MPX cases experiences mild to moderate symptoms. The severity of disease varies depending on the transmission route, host susceptibility, and the quantity of virus inoculated, with invasive modes of exposure causing more severe disease and a shorter incubation period [9].

Usually, the incubation period for MPX is 6 to 13 days, but can range from 5 to 21 days. Human MPX often begins with a combination of the following symptoms: fever, headache, chills, exhaustion, asthenia, lymph node swelling, back pain, and muscle aches. Commonly, within three days of the onset of these prodromal symptoms, a centrifugal maculopapular rash starts at the site of the primary infection and rapidly spreads to other parts of the body. Rash dissemination with palms and soles involvement is characteristic of MPX. The lesions progress, usually within 12 days, simultaneously from the stage of macules to papules, vesicles, pustules, crusts, and scabs (monomorphism). This is different in chickenpox (varicella), where progression of exanthema is more varied with simultaneous presence of different stage of rush elements (false polymorphism). The lesions may be centrally depressed and can be extremely itchy, and secondary bacterial infection may occur if scratching occurs. Lesions on oral or ophthalmic mucosa (enanthema) may also be present. Prior to and concomitant with the rash, lymphadenopathy is observed in many patients [8].

However, in the 2022 outbreaks, many cases presented with rashes in the anogenital region. The number of lesions may range from a few to thousands. According to the WHO update report, 81% had a widespread body rash, 50% were febrile and 41% presented with genital rash. For most affected people, MPX is a self-limited disease, typically lasting two to four weeks and ending in full recovery [1,8].

Complications in endemic countries include encephalitis, secondary skin bacterial infections, dehydration, conjunctivitis, keratitis, and pneumonia. The case fatality rate (CFR) of MPX ranges from 0% to 11% in outbreaks in endemic areas, with mortality mostly affecting young children [8]. Immunocompromised individuals are especially at risk of severe disease [10]. In the outbreak in Nigeria in 2017, patients with concurrent HIV infection had more severe morbidity with more skin lesions and associated genital ulcers compared to HIV-negative individuals. No deaths were reported among HIV-positive patients [11]. In Nigeria, between September 2017 and 5 June 2022, 257 confirmed cases were identified, including nine deaths (CFR = 3.5%), at least five of which were immunosuppressed [12,13]. Major disease sequelae are usually disfiguring scars and permanent corneal lesions.

Any individual meeting the clinical definition for a suspected case should be offered testing. Additionally, risk factors for infection, such as being a gay, bisexual and other MSM, reporting a high number of sexual partners in the prior three weeks, and having attended a gathering where a confirmed case was reported can be suggestive of the need to test for MPXV [3].

The primary diagnostic test for MPX diagnosis is PCR of the skin lesion material. In addition, other specimens such as an oral, nasopharyngeal or rectal swab may also be collected, as appropriate [1-3].

Clinical management of patients with suspected or confirmed MPX requires early recognition through screening protocols adapted to local settings, prompt isolation and rapid implementation of appropriate infection prevention and control (IPC) measures, testing to confirm diagnosis, symptomatic management of patients with mild or uncomplicated MPX, and monitoring and treatment of complications and life-threatening conditions, such as progression of skin lesions, secondary bacterial infection of skin lesions, ocular lesions, and rarely, severe dehydration, severe pneumonia or sepsis [3].

Patients with mild or uncomplicated MPX who are isolated at home require careful assessment of the ability to safely isolate and maintain required IPC precautions in their home to prevent transmission to other household members, and have access to care if the condition progresses or worsens. Precautions should remain in place until lesions have crusted, scabs have fallen off and a fresh layer of skin has formed underneath [1].

Current treatment of MPX is symptomatic (alleviation of fever and pruritus, hydration), including prevention and treatment of secondary bacterial infections. Few antiviral drugs, such as tecovirimat, brincidofovir and cidofovir are potential options for severe cases [19]. Only tecovirimat has market authorization in the EU for the treatment of orthopoxvirus infection, including MPX. Limited data on efficacy and safety exist currently, while clinical studies are ongoing in Africa [20].

Previous vaccination against smallpox can confer cross-protection against MPX, which was estimated from older studies to be as high as 85% [2]. The protective effect of smallpox vaccination can last more than 20 years. However, despite the waning effect smallpox vaccine confers, it is believed that memory B and T cells can provide lifelong protection against severe disease, therefore some degree of protection should be expected in the adult population in the EU/EEA who is currently over 50 years [21]. During the 2022 outbreak, some countries made vaccination recommendations [1]. Early post-exposure vaccination (within four days of exposure to a MPX case) with smallpox vaccine (off-label use) may prevent the disease or make its course less severe [18].

In conclusion, the emergence of new zoonoses and their potential spread at the global level is something we need to be prepared for. In the face of deforestation, migration and conflict, contact between human populations and wildlife is becoming more common, and such proximity will favor spillover of zoonotic pathogens [4].

Whereas during the ongoing multi-country outbreak of MPX, sexual contact was identified as the most commonly suspected and reported route of transmission, the sensitivity in reporting a full list of sexual contacts made it challenging to break all chains of transmission. At this stage, WHO recommends that all known contacts or individuals who believe they may have been exposed monitor their symptoms for 21 days from the last known or suspected contact with a case. Testing and quarantine are required for persons with clinical manifestation of MPX. In the absence of symptoms among contacted, they are recommended to [3]:

- follow hand hygiene
- rigorously practice respiratory etiquette
- avoid contact with children or immunocompromised individuals or pregnant women
- avoid any form of sexual contact for 21 days
- avoid non-essential travel.

The HCWs should apply standard precautions and perform a risk assessment to evaluate the need to use transmission-based precautions. Standard precautions include: hand and respiratory hygiene, personal protective equipment, aseptic technique, safe injections and sharps injury prevention, environmental cleaning and disinfection, proper handling of laundry and linen, decontamination and reprocessing or reusable patient care items and equipment, and waste management, and should be used for all patients at all times [3].

Pre-exposure or post-exposure prophylaxis by using smallpox or monkeypox vaccines should rely on clinical decision-making between health care provider and prospective vaccinee, based on a joint assessment of risks and benefits, on a case-by-case basis.

What is currently missing is knowledge of what pathogens might emerge and an adequate investment in surveillance [4].

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