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The Outbreak of Human Monkeypox in 2022: A Changing Epidemiology or an Impending Aftereffect of Smallpox Eradication?

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This article presents a concise mini review about human monkeypox (MPX), in response to the current outbreak in non-endemic countries. MPX is one of the viral zoonotic diseases which is attributed to monkeypox virus (MPXV) and causes a smallpox-like disease. Despite its ability to infect various mammals, the animal reservoir for MPXV is still unconfirmed. The disease usually lasts for an average of 2-4 weeks before complete recovery. The incubation period for MPXV ranges from 5-21 days and the illness starts with prodromal phase, which is characterized by fever, chills, muscle pain, back pain, general malaise, lymph node enlargement, and headache, followed by rash. MPX is a self-limited illness with spontaneous recovery in most cases. In the middle of May 2022, an outbreak of human MPX has been declared by the World Health Organization (WHO) across various WHO regions, and in countries that are not endemic for the disease. As of June 08, 2022, the number of confirmed MPX cases that were reported across 18 countries of European Union/European Economic Area (EU/EEA) has reached 704 cases. Worldwide, and as of June 08, 2022, a total of 1285 confirmed MPX cases were reported in non-endemic countries across four WHO regions. Exportation of MPXV from Africa to other continents has been increasingly reported. Lacking travel connections to Africa among most current reported cases in 2022 raises an alarm about the changing epidemiology of the disease which warrants a stringent epidemiological surveillance to prevent further escalation of the current outbreak in non-endemic countries.

Keywords: human monkeypox, outbreak, smallpox, eradication, DRC, *Orthopoxvirus*, MPXV

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BACKGROUND

Monkeypox (MPX) is characterized as one of the vesiculopustular viral zoonotic diseases which is attributed to monkeypox virus (MPXV), a double-stranded DNA virus, and causes a smallpox-like disease (1). MPXV was initially discovered in monkeys at a Danish laboratory back in the 1950s, which then caused the first human MPX case in the Democratic Republic of Congo (DRC) in 1970 (2), and repeatedly under survey in DRC since the 1980s with multiple cases/epidemic. MPXV is one of the pathogenic viruses for humans that falls under *Poxviridae* family, and the genus of *Orthopoxviruses*. Along with MPXV, the *Orthopoxviruses* genus includes another three pathogenic

viruses for humans, namely, Variola virus (smallpox), Cowpox virus, and Vaccinia virus (1, 3). Despite its ability to infect various mammals, the animal reservoir for MPXV is still unconfirmed (2). However, it was reported in the literature that MPXV was successfully isolated twice from wild animals, including, a rope squirrel, and a sooty mangabey in DRC and Ivory coast, respectively (3). Although several animals (monkeys, rope squirrels, sun squirrels, pouched rats, and dormice) have been suspected to serve as a host reservoir for MPXV (4, 5), the arboreal squirrels (*Funisciurus anerythrus*) are considered as a primary reservoir being first mammal species from which the MPXV has been isolated in nature (6). Overall, two distinct genetic clades of MPXV were identified, including, the West African clade and the Congo Basin (Central African) clade (7).

The first reported case of human MPX goes back to 1970 in the DRC (8), and was further reported in multiple African countries in western and central Africa, as well as outside the African continent (1, 2, 9, 10). Although the first reported case was in DRC, MPXV might have already existed in other western and central African countries at the same time, with low level of detectability due to the countries' focus on smallpox and its eradication, and the environmental suitability for MPXV in western and central Africa. Besides, the first human MPX outbreak outside Africa was reported in the United States of America (US) in 2003 (2, 11), and was attributed to wild rodents imported from Ghana (12, 13). Since the global eradication of Variola virus (the causative agent of smallpox) in 1980, and the cessation of routine smallpox vaccination programs, it has been noticed that infections with MPXV are sporadically and increasingly reported, especially among those who are not vaccinated with smallpox vaccine (2). Additionally, the literature reported that vaccination with Vaccinia virus (*Orthopoxvirus*) provided 85% protectivity against MPXV (1, 14).

CLINICAL FEATURES AND TRANSMISSION

MPXV results in a smallpox-like disease, but with milder symptoms compared to smallpox. This vesiculopustular disease was found to last for an average of 2-4 weeks before complete recovery (13). The incubation period for MPXV ranges from 5-21 days and the illness starts with prodromal phase which is characterized by fever, chills, muscle pain, back pain, general malaise, and headache (7, 13, 15). A key distinguishing feature between MPX and smallpox is that the earlier causes lymph node enlargement (lymphadenopathy) (12, 13). Few days after the onset of the above-mentioned symptoms, the rash starts to develop which passes through five distinct stages: macules, papules, vesicles, pustules, and scabs. The rash usually starts in the face then spreads into other body parts, especially the extremities. Animal to human, and human to human transmission have been identified in the literature (1, 2, 13, 16). Zoonotic animal to human transmission may occur through direct contact with infected animals (e.g., bites, scratches), or indirect contact with infected animal fluids or lesion materials. Human to human transmissions were identified to occur through direct contact with infected person (e.g., respiratory droplets, exposure to infection lesions or body fluids) (1, 17). Additionally, indirect contact with lesion materials through contaminated inanimate objects (e.g., contaminated cloths or linens) may be counted as a possible route to contract the illness (13). Moreover, vertical transmission (mother to foetus) should be also considered (15, 18)

DIAGNOSIS, MANAGEMENT, AND POSSIBLE COMPLICATIONS

Further to the clinical presentation of the patient, and the pathognomonic feature of MPX which differentiates it from chickenpox or smallpox i.e., Lymphadenopathy, Polymerase Chain Reaction (PCR) and genome sequencing is used to confirm the viral existence in samples from MPX lesions (vesicle fluid or scabs) (2, 12, 19, 20). Further diagnostic tests include, virus isolation and culture, electron microscopy examination, and immunohistochemistry for the presence of Orthopoxvirus- specific antigens in biopsy tissues (12, 14). However, PCR for blood samples is inconclusive. Also, due to antigenic cross-reactivity among various Orthopoxviruses, and considering the fact that antibodies develop later, serological tests (Anti-Orthopoxvirus IgG, and Anti-Orthopoxvirus IgM) are not recommended for diagnosis or case detection (14). However, serological tests can be helpful for retrospective purposes when examining previous exposure to Orthopoxvirus, including a pathogen or smallpox vaccination (14).

MPX is a self-limited illness with spontaneous recovery in most cases. Conservative management to alleviate symptoms is needed. Additionally, tecovirimat which is an antiviral agent for smallpox, can be used also for human MPX as it was recently approved by the European Medical Association (11), despite lacking data on its effectiveness in treating human MPX (13). For the purposes of containing MPX outbreak, the US Centres for Diseases Prevention and Control (CDC) suggests the use of Vaccinia Immune Globulin (VIG), smallpox vaccine, tecovirimat and cidofovir (antivirals) (13). Nevertheless, most of the aforementioned options are lacking data on their effectiveness in treating human MPX and should be administered in a high caution as Investigational New Drug (IND) (12, 13).

In a recent systematic review (1), and across all countries included in the analysis, case fatality rate of Human MPX was estimated to be around 8.7%. Specifically, case fatality rate for the Central African clade and the West African clade was identified to be 10.6% and 3.6%, respectively (1). Also, mortality is found to be higher among young children (11). Despite being a self-limited disease, some complications may occur such as bronchopneumonia, secondary bacterial infection, encephalitis, corneal infection, and sepsis (11).

A BRIEF OVERVIEW ON HISTORICAL AND CURRENT OUTBREAKS

Following the first confirmed case of human MPX in 1970 which was reported in DRC, MPX was sporadically reported in small

and large outbreaks. In 2003, the first human MPX cases were confirmed in the US with an outbreak that resulted in more than 70 cases (3, 11). Also, a large outbreak of human MPX caused by the West African clade was declared in Nigeria in October 2017, with around 146 suspected cases and 42 confirmed cases (20). Later, human MPX cases were reported in Israel (2018), UK (2018, 2019, 2021, and 2022), Singapore (2019), and the US (2021) as a result of exportation of MPXV from the African continent (10, 11). For a more detailed information about the historical outbreaks of human MPX, we recommend the following resource (3). Moreover, the human MPX activity is alarming especially in multiple African countries and prior to the declaration of the current human MPX wave in non-endemic countries outside the African continent. For example, the number of confirmed and suspected human MPX cases that were reported in eight African countries from January 2022 and as of June 08, 2022 is 59 and 1536, respectively, with an associated death toll which reached 72 fatalities in the same period (21).

In the middle of May 2022, an outbreak of human MPX has been declared by the World Health Organization (WHO) across various WHO regions, and in countries that are not endemic for the disease. As of June 08, 2022, the number of confirmed MPX cases that were reported across 18 countries of European Union/European Economic Area (EU/EEA) has reached 704 cases (22). Worldwide (including EU/EEA), and as of June 08, 2022, a total of 1285 confirmed MPX cases were reported in non-endemic countries across four WHO regions (21). So far, and of the present 2022 MPX wave, the vast majority of laboratory-confirmed MPX cases were reported in the WHO European region (n=1112), followed by Region of the Americas (n=153), Eastern Mediterranean Region (n=14), and Western Pacific Region (n=6) (21). As of the time of writing this paper, there were no reported deaths during the current MPX outbreak in non-endemic countries. Country wise and as of June 10, 2022, most confirmed human MPX cases of the current MPX wave in non-endemic countries were reported in the United Kingdom (n= 366), followed by Spain (n= 275), Portugal (n= 209), Germany (n= 165), Canada (n= 116), France (n= 91), Netherlands (n= 60), and the United States (n= 48) (23). In the WHO Eastern Mediterranean Region, human MPX cases were reported in the United Arab Emirates (n=13), followed by Israel (n=4), and Morocco (n= 1) (23).

Efforts are being invested in epidemiological surveillance and contact tracing, which found that most cases are confirmed among young men who have sex with men and among people with no travel links to endemic countries (24, 25). The WHO is raising concerns to inform readiness, risk assessment, and response in case of a large scale global spread of human MPX (7).

PREVENTION

As a global public health issue, prevention plays an important role in controlling infectious diseases outbreak. Vaccination against smallpox has shown up to 85% protectivity against human MPX infection as well (1, 15). Despite that old generation smallpox vaccine is not available, the newly modified one based on Vaccinia virus (attenuated two-dose vaccine) has been approved in 2019 for the prevention of MPX (11). Moreover, practicing precautionary protective measures that reduce zoonotic and human to human transmissions are of paramount importance (1, 12).

SHOULD THE WORLD WORRY?

It seems that the Coronavirus Disease – 2019 (COVID-19) pandemic has put the world into a consistently alert situation due to the pandemic associated health, socioeconomic and political consequences. Unlike SARS-CoV-2, MPXV may not go clinically unnoticed as often as COVID-19 (15). Most individuals infected with MPXV are symptomatic, however, asymptomatic (subclinical) infections were also identified and reported in the literature (26, 27). Additionally, the transmission of MPXV is primarily through large respiratory droplets which travel for few distance in the air (unlike aerosols), thus, requires close and prolonged face to face exposure with a lower ability to infect large group of people in contrast to SARS-CoV-2 which can be transmitted through aerosols (15). Also, another risk to contract the illness is the exposure to virally contaminated body fluids or lesion materials (e.g., from infected persons) which will be obviously noticed on patients unlike asymptomatic SARS-CoV-2 infections (28). Nevertheless, and despite low transmissibility of MPXV compared to SARS-CoV-2, the scenario of potential genetic mutations affecting MPXV could have a role in explaining the unprecedented current outbreak of human MPX in non-endemic countries, in which these mutations may contribute to a higher transmissibility or a hard-to-trace slow transmission (15). For instance, among the currently identified human MPX cases in the United States (US), the US CDC reported that genetic sequencing revealed at least two distinct strains of MPXV that are involved in the current outbreak in the US. The CDC has genetically sequenced a total of 10 viruses sampled from recent human MPX cases in the US (two from 2021, and eight from 2022), and found that three viruses are genetically different from what was sequenced in Europe during the current MPX wave (29). This raises concerns about a suspected wider international spread that was not realized before. Therefore, genetic sequencing of the "new strains" isolated from non-endemic countries is essential to be done and considered the only way to clarify the origin of these strains. The lack of identified epidemiological links to West or Central Africa among most current human MPX cases in non-endemic countries in 2022, does not rule out any contact with subclinical cases of travellers or animals. As this is not yet clear, the world might have a major problem of an emerging and wider MPX spread in the Palearctic realm.

Additionally, a recent systematic review pointed to a possible changing epidemiology of human MPX over the past decades (1). A declining immunity among people, halting routine vaccination against smallpox after its eradication in the 1980s, and ecological

factors are all possible causes for the resurgence of human MPX cases (1, 2, 30, 31).

Due to similarity between the eradicated smallpox virus and MPXV, the already known smallpox vaccine and antivirals may play essential role in providing prevention and treatment for MPX cases without delay, unlike the emerging SARS-CoV-2 for which the scientific community needed much time to produce an effective vaccine and antiviral treatment (2, 11, 28). On the other hand and looking at the current outbreak of MPX in non-endemic countries, the scientific community cannot rule out the possibility of aerosols spread of MPXV, which may act as a potential threat for a new pandemic era.

FINAL REMARKS

Human MPX is one of the emerging zoonotic diseases that is primarily endemic in many African countries, especially in central and western Africa. Exportation of MPXV from Africa to other continents has been increasingly and sporadically reported. Looking at the current MPX outbreak in non-endemic countries and considering the lack of identified epidemiological links to West or Central Africa among most current reported cases in 2022, this outbreak raises an alarm about the changing epidemiology of the disease which warrants a stringent epidemiological surveillance to prevent further escalation of the current outbreak in non-endemic countries.

AUTHOR CONTRIBUTIONS

AA-T conceived the idea and wrote the initial draft of the manuscript. RA and SA were involved in the preparation of part of the initial draft. All authors have critically revised, read and approved the manuscript for submission.

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