SUBMITTED 27 JUN 22
REVISION REQ. 20 JUL 22; REVISION RECD. 25 JUL 22
ACCEPTED 3 AUG 22
ONLINE-FIRST: AUGUST 2022
DOI: https://doi.org/10.18295/squmj.8.2022.046

Monkeypox Outbreak

More queries posed as cases globally soar

***Salah T. Al Awaidy,[1] Faryal Khamis,[2] Malik Sallam,[3] Ramy M. Ghazy,[4] Hassan Zaraket[5]**

[1]Office of Health Affairs, Ministry of Health, Muscat, Oman; [2]Adult Infectious Diseases, Department of Medicine, Royal Hospital, Ministry of Health, Muscat, Oman; [3]Department of Pathology, Microbiology and Forensic Medicine, School of Medicine, the University of Jordan, Amman, Jordan; [4]High Institute of Public Health, Alexandria University, Egypt; [5]Department of Experimental Pathology, Immunology and Microbiology, American University of Beirut, Lebanon.
**Corresponding Author's e-mail: salah.awaidy@gmail.com*

Introduction

Emerging and re-emerging infectious diseases outbreaks are on the rise, with devastating effects on people's health, society, and economy.[1] An outbreak of human monkeypox (HMPX) in multiple non-endemic countries has been announced by the World Health Organization (WHO) in early May 2022 with the majority of cases having no confirmed travel to endemic countries.[2] The causative agent, monkeypox virus (MPXV), was isolated for the first time in 1958 by the Staten's Serum Institute in Copenhagen, Denmark.[3] The virus is classified as a species within the *Orthopoxvirus* genus together with variola virus, the causative agent of smallpox.[4] The MPXV causes similar, albeit less severe clinical manifestations compared to smallpox with lower case-fatality rate (CFR).[4]

Monkeypox is considered a zoonotic disease, being transmitted from animals to humans with limited chains of human-to-human transmission.[5] The HMPX cases were frequently detected near tropical rainforests, the habitat of a variety of animals known to harbour MPXV.[5]

Examples of these animals include squirrels, Gambian rats, dormice, monkeys of various species, among other animals; however, the definitive animal reservoir of MPXV remains unknown.[4,5] Prior to the current outbreak in non-endemic countries, HMPX has been endemic in Central and West Africa.[4] Occasional outbreaks outside Africa were linked to history of travel or imported animals from endemic regions.[4,5]

The HMPX is a contagious infection that leaves a distinctive rash, following exposure via close contact with an infected animal's bodily fluids or through a bite. It can also be acquired through preparation of bush meat or with infectious sores, scabs, or body fluids (in human-to-human transmission), or through respiratory secretions. The incubation period ranges from 5 to 21 days.[6,7] The prodromal phase, which may not manifest in all cases, resembles influenza illness and includes fever, headache, backache, lymphadenopathy and fatigue.[8] Following the prodrome, the affected individuals develop a rash, initially macular that evolves to papules, vesicles then pustules within 1-5 days.[6] The skin lesions could be present on the hands, feet, chest, face, genitalia or the anus.[6,8] Before healing, the pruritic skin lesions evolve through a number of phases, eventually forming scabs.[8] Enanthems could occur as well, involving the mouth, vagina or anus.[8] Complications such as sepsis, pneumonia, bacterial super-infection, vision loss, skin scarring, encephalitis, dehydration, skin pigmentation, and death may occur.[9] The smallpox vaccines used in the past are 85% effective in preventing HMPX, however, its use has ceased since the eradication of smallpox.[10] More recently, a novel two-dose vaccine based on the modified attenuated Vaccinia virus was approved. In addition, antivirals such as tecovirimat, which was licensed by the European Medicines Agency (EMA) in 2022, are available, albeit with limited or no human safety and efficacy data.[11]

Global burden of HMPX

Before the ongoing 2022 HMPX outbreak, a majority of infections that were reported in the endemic regions were caused by animal to human spillover, with rare cases of human-to-human transmission that primarily involved household contacts.[7] However, the present epidemic serves as a reminder of how viruses capable of sustained human transmission can emerge suddenly.[12]

Until recently, HMPX was limited to West and Central Africa, where the virus can be found in several animal species.[5,13] and dominated by two separate clades, one of which is exclusive to the Congo Basin and the other is prevalent in West Africa.[4] The Congo Basin lineage is

expected to be more contagious and has historically been associated with more severe illness and a higher case fatality rate (CFR, 10.6% 95% CI 8.4-13.3%).[4, 11]

It has been confirmed that the West African clade is indeed the clade associated with the current HMPX outbreak and is characterized by a lower CFR (3.6%, 95% CI 1.7 – 6.8%).[14] An important and urgent call for modification of the MPXV clades' nomenclature has been advocated to make it non-discriminatory and non-stigmatizing with reliance on Arabic numerals for clade assignment rather than geographic location.[15]

The cumulative number of confirmed HMPX cases that have been reported to WHO exceeded 3500 and one fatality reported from 50 countries between April and till 27 June 2022.[16] These cases were reported in four different WHO regions namely the Region of the Americas, the European, Eastern Mediterranean, and Western Pacific Regions in countries where MPXV is not endemic.[16] The vast majority of confirmed HMPX cases were reported from the WHO European Region and the Region of the Americas [Figure 1].

The second meeting of WHO held on 23 June 2022, concurred with the International Health Regulations (IHR) Emergency Committee that multi-country monkeypox outbreak does presently constitute a Public Health Emergency of International Concern (PHEIC). The current ongoing HMPX outbreak presents a moderate danger to global public health according to the WHO.[2] Contrary to the previous HMPX cases in the endemic regions, no linkages to animals have been traced amid the ongoing outbreak, and the initial cases were reported in Europe, which may hint that the virus could have been circulating between people for months unnoticed.[6,18]

Since the first recorded case in April 2022, no fatalities have been recorded so far amid the ongoing outbreak in previously non-endemic countries as a result of the disease.[2] Males make up the majority of confirmed cases of monkeypox, and the majority of these cases were among males who have sex with males (MSM) in densely populated metropolitan settings.[2] In addition, more cases of HMPX have been recorded in the WHO African Region, where the disease is endemic with 1536 suspected cases since the start of the year 2022, of which 59 cases have been confirmed and 72 fatalities have been recorded.[2] Worth mentioning that contrary to the relatively high case fatality rate in Africa, the lack of fatalities in the current outbreak outside Africa could be linked to early detection of cases and quality of health care including the use of antivirals and prophylactic vaccines.

The ongoing detection of the virus and the reported deaths in several African countries underpin the urgent need to better understand the source and the transmission dynamics of the diseases and to provide people with the knowledge and resources they need to safeguard themselves and others in a variety of situations.

Measures needed to mitigate and stop the spread.

The public health hazards of HMPX is on rise, with ongoing transmission of the virus and potential spread to people at higher risk of development of severe illness, such as pregnant women, young children and those with impaired immune systems (immune-compromised individuals), as virus seizes the opportunity to establish itself as a resident human pathogen.[19]

In the context of the current multi-country HMPX outbreak, and at this stage, it is vital to establish reliable and efficient surveillance at a national level, since failure to do so raises the risk of undetected cases and uncontrolled spread of the outbreak to additional regions/countries.

Another issue to be considered is that the majority of cases have been reported among MSM or in healthcare settings. Therefore, the countries are recommended to seek out overlooked cases while conducting contact tracing. Testing and identification of suspected cases are essential to monitor the progress of the outbreak and to direct the vaccination programs. [20]

Moreover, since a majority of emerging infectious disease incidents that afflicted humans in the recent era were zoonotic in nature, the importance of proactive zoonotic and animal surveillance activities should be highlighted.[20]

Regarding the utility of smallpox vaccinations for the prevention of HMPX, the WHO released interim recommendations, stating that vaccination should only be used when necessary and does not advocate widespread HMPX immunization.[21] To learn more about the effectiveness of vaccines as they are used in the current situation, the countries are required to cooperate in the adoption of standardized research protocols tackling this aim.

The WHO endorsed the use of vaccines in the fight against the outbreak. Vaccination of contacts cases, and post-exposure prophylaxis (PEP) including health care workers, researchers dealing with orthopoxviruses, and clinical lab technicians to be provided

preferably within four days of the initial exposure, in order to avoid the start of illness in these contacts.[21]

In addition to the need of information on HMPX vaccinations and their usage recommendations for exposed individuals, as well as antivirals and the necessity of deploying these vaccines and antivirals where they are required. In January 2022, the European Medicines Agency authorized tecovirimat, an antiviral originally designed to fight monkeypox, for the treatment of monkeypox. In the context of a monkeypox epidemic, there is a limited of experience with these therapies.[21] Additionally, it is crucial to improve laboratory and diagnostic capabilities, clinical management, and measures to prevent and control infection in health care and community settings.

Conclusions and the way forward

The rapid transmission of HMPX and its widespread detection in various countries worldwide can be viewed as an emergency of international concern.[2] The current multi-country outbreak of the disease is evolving, with potential risk of further spread if swift containment interventions are not promptly devised and followed.

The CFR observed in the African region in contrast to what we are seeing outside of Africa outbreak highlights the need for assistance involving all response components, including but not limited to community awareness-raising, risk communication, human and animal surveillance, diagnostic and laboratory assistance, and regional research and analysis of antivirals and vaccines. This is critical to curb the current outbreak but also prevent future ones at their source. Countries that have recently been impacted by HMPX and those that have experienced it for a long time need vigilant intervention measures.

To contain MPXV transmission, we call for an urgent action to interrupt the chains of virus spread in non-endemic and endemic countries. A special attention should be focused on ensuring effective surveillance in highly vulnerable groups in terms of exposure or disease severity with cautious approach to avoid potential stigmatization of these groups.[22] Currently, global and regional public health authorities are recommended to: (1) amend the law to enable it to list HMPX as a notifiable disease; (2) ensure robust surveillance with emphasis of zoonotic disease surveillance in place by all countries, including appropriate contact-tracing, isolation and care of patients; (3) call for immediate involvement by the national advisory committees and panels of scientific experts and groups to formulate the

roadmap necessary to limit and contain the threat of HMPX. The WHO recommends that potential cases should be reported immediately and investigated within 48 hours; and the health professionals need to be aware and involved in the developing epidemic management framework that has proven successful in other contexts for effective planning and response owing to the nature of disease propagation in an outbreak environment.[23]

Without increased and efficient efforts, we run the risk of the progress we have made toward controlling this illness worldwide. Collaborative efforts especially at the national levels are urgently needed worldwide to provide accurate and reliable information about the disease to the general population as well as to most-at-risk group which can help to halt the virus spread.

Authors' Contribution

SA, FK generated the idea. SA, FK, MS, RG and HZ designed and structured the manuscript. SA, MS, HZ, RG and FK drafted the manuscript. SA, MS, RG, HZ and FK performed the literature review and information extraction. SA, FK, MS, RG and HZ revised and critically reviewed the manuscript. All authors approved the final version of the manuscript.

References

1. Baker RE, Mahmud AS, Miller IF, Rajeev M, Rasambainarivo F, Rice BL, et al. Infectious disease in an era of global change. Nature Reviews Microbiology. 2022/04/01 2022;20(4):193-205, doi:10.1038/s41579-021-00639-z.

2. WHO | World Health Organization. Multi-country monkeypox outbreak: situation update. From: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON390 Accessed: June 2022.

3. Magnus Pv, Andersen EK, Petersen KB, Birch-Andersen A. A POX-LIKE DISEASE IN CYNOMOLGUS MONKEYS. Acta Pathologica Microbiologica Scandinavica. 1959;46(2):156-176, doi:https://doi.org/10.1111/j.1699-0463.1959.tb00328.x.

4. Bunge EM, Hoet B, Chen L, Lienert F, Weidenthaler H, Baer LR, et al. The changing epidemiology of human monkeypox—A potential threat? A systematic review. PLOS Neglected Tropical Diseases. 2022;16(2):e0010141, doi:10.1371/journal.pntd.0010141.

5. Rimoin Anne W, Mulembakani Prime M, Johnston Sara C, Lloyd Smith James O, Kisalu Neville K, Kinkela Timothee L, et al. Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo.

Proceedings of the National Academy of Sciences. 2010/09/14 2010;107(37):16262-16267, doi:10.1073/pnas.1005769107.
6. Vivancos R, Anderson C, Blomquist P, Balasegaram S, Bell A, Bishop L, et al. Community transmission of monkeypox in the United Kingdom, April to May 2022. Eurosurveillance. 2022;27(22):2200422, doi:doi:https://doi.org/10.2807/1560-7917.ES.2022.27.22.2200422.
7. Nolen LD, Osadebe L, Katomba J, Likofata J, Mukadi D, Monroe B, et al. Extended Human-to-Human Transmission during a Monkeypox Outbreak in the Democratic Republic of the Congo. Emerg Infect Dis. 2016;22(6):1014-1021, doi:10.3201/eid2206.150579.
8. Minhaj FS, Ogale YP, Whitehill F, et al. Monkeypox Outbreak — Nine States. MMWR Morb Mortal Wkly Rep. 2022;2022(71):764–769, doi:10.15585/mmwr.mm7123e1.
9. Beer EM, Rao VB (2019) A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. PLOS Neglected Tropical Diseases 13(10): e0007791. https://doi.org/10.1371/journal.pntd.0007791
10. WHO | World Health Organization. Monkeypox fact sheet. From: https://www.who.int/news-room/fact-sheets/detail/monkeypox Accessed: July 2022.
11. Saxena SK, Ansari S, Maurya VK, Kumar S, Jain A, Paweska JT, Tripathi AK, Abdel-Moneim AS. Re-emerging human monkeypox: A major public-health debacle. J Med Virol. 2022 Jun 1. doi: 10.1002/jmv.27902. Epub ahead of print. PMID: 35652133.
12. Sklenovská N, Van Ranst M. Emergence of Monkeypox as the Most Important Orthopoxvirus Infection in Humans. Frontiers in Public Health. 2018-September-04 2018;6, doi:10.3389/fpubh.2018.00241.
13. Bunge EM, Hoet B, Chen L, Lienert F, Weidenthaler H, et al. (2022) The changing epidemiology of human monkeypox—A potential threat? A systematic review. PLOS Neglected Tropical Diseases 16(2): e0010141. From: https://doi.org/10.1371/journal.pntd.0010141
14. Selhorst P, Rezende AM, de Block T, Coppens S, Smet H, Mariën J, et al. Belgian case of Monkeypox virus linked to outbreak in Portugal. 2022; From: https://virological.org/t/belgian-case-of-monkeypox-virus-linked-to-outbreak-in-portugal/801. Accessed: June 2022.
15. Happi C, Adetifa I, Mbala P, Njouom R, Nakoune E, Happi A, et al. Urgent need for a non-discriminatory and non-stigmatizing nomenclature for monkeypox virus. From: https://virological.org/t/urgent-need-for-a-non-discriminatory-and-non-stigmatizing-nomenclature-for-monkeypox-virus/853 Accessed June 2022.

16. WHO | World Health Organization. Multi-country monkeypox outbreak: situation update. From: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON396 Accessed: June 2022

17. WHO | World Health Organization. The global distribution of human monkeypox. From: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON396. Accessed July 2022.

18. Adler H, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. The Lancet Infectious Diseases. 2022, doi:10.1016/S1473-3099(22)00228-6.

19. Reynolds MG, Damon IK. Outbreaks of human monkeypox after cessation of smallpox vaccination. Trends Microbiol. 2012/02/01/ 2012;20(2):80-87, doi:10.1016/j.tim.2011.12.001.

20. WHO | World Health Organization. Questions and answers for monkeypox. From: https://www.who.int/news-room/questions-and-answers/item/monkeypox?gclid=CjwKCAjwrNmWBhA4EiwAHbjEQM3ca4RCOhXBks5pD65waOwNH7YVkP4-s9sFMGDwqPbU0iZuQQZKThoCIOgQAvD_BwE Accessed: July 2022.

21. WHO | World Health Organization. Vaccines and immunization for monkeypox: Interim guidance, 14 June 2022. From: https://www.who.int/publications/i/item/who-mpx-immunization-2022.1 Accessed: June 2022.

22. Bragazzi NL, Khamisy-Farah R, Tsigalou C, Mahroum N, Converti M. Attaching a stigma to the LGBTQI+ community should be avoided during the monkeypox epidemic. Journal of Medical Virology. 2022/06/02 2022;n/a(n/a), doi:https://doi.org/10.1002/jmv.27913.

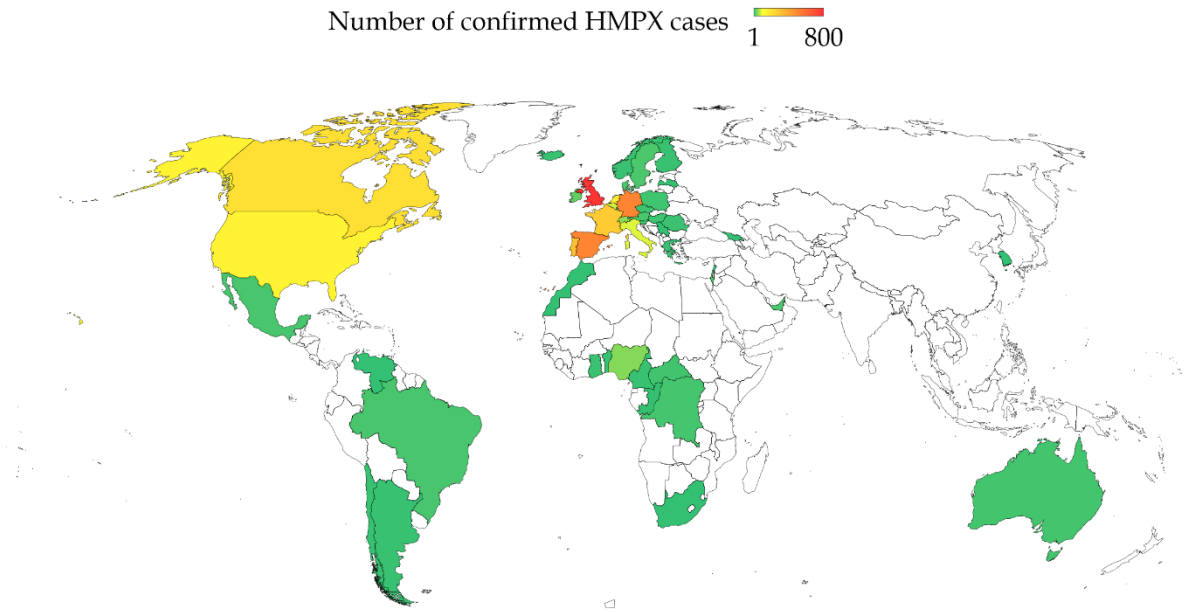

Figure 1: The global distribution of human monkeypox (HMPX) cases as of 27 June 2022.[17]