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## Correspondence



## Unexpected sudden rise of human monkeypox cases in multiple non-endemic countries amid COVID-19 pandemic and salient counteracting strategies: Another potential global threat?

Dear Editor,

Very recently, since May 13, 2022, multiple cases of monkeypox have been identified and reported to the World Health Organization (WHO) in nearly 12 non-African countries that are not endemic for monkeypox virus [1,2]. Monkeypox disease is endemic and normally limited to West and Central Africa, however its epidemiology has been reported to be changing and evolving in the last few years with cases being reported in other few countries beyond Africa [3–8]. The current situation of rising cases is evolving continuously and as surveillance and monitoring of monkeypox virus infection will expand in non-endemic countries then more cases will be identified, which could pose an eminent global public health threats [2].

Monkeypox virus is an enveloped double-stranded DNA virus which belongs to *Orthopoxvirus* genus in the family Poxviridae, the same family as of smallpox virus, and has two clades - the West African clade and the Congo Basin (Central African) clade [7]. This zoonotic virus was first detected in monkeys in a Danish laboratory in the year 1958, therefore named as monkeypox, and its first human case was recognized in a child in the Democratic Republic of the Congo in 1970 [1,2,9,10]. Since then, such cases are continuously reported from different regions of Central and West Africa. Seventy (70) cases of monkeypox were first noticed in the USA in the year 2003 and were linked to infected pet prairie dogs housed with dormice and Gambian pouched rats imported from Ghana. That was the first monkeypox outbreak identified outside of Africa [9]. A large monkeypox outbreak of ~ 500 suspected and ~ 200 confirmed cases was reported in Nigeria since 2017 with a Case Fatality Rate (CFR) of ~ 3%. The CFR may be higher among young children. Monkeypox was also reported in the persons who travelled from Nigeria to different countries mainly Israel (2018), the United Kingdom (2018, 2019, 2021, 2022), Singapore (2019), and the USA (2021). The epidemiology of human monkeypox virus is changing, and its frequency and geographic circulation in West and Central Africa are reported to be increased in past few years, as less than 40 years age people have less cross-protective immunity during the smallpox post-eradication era [3,5–7,11]. Very recently, in May 2022, multiple cases of monkeypox virus infection have been reported from nearly 12 non-endemic countries [1]. As of 21 May, 92 laboratory confirmed cases, and 28 suspected cases of monkeypox have been reported from Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, United Kingdom (UK), United States of America (USA), with most of the cases from UK, Portugal and Spain [2]. No monkeypox virus associated death has yet been reported from these countries. As per the recent news reported on May 23, 2022 another three countries namely Israel, Switzerland and Austria confirmed the monkeypox cases in their countries (<https://www.bbc.com/news/health-61540474>).

The clinical presentation of monkeypox resembles that of smallpox,

although it is critically less severe. However, smallpox was more easily transmitted and comparatively more often fatal (30% of patients died). The incubation period of this rare viral disease monkeypox is usually 6–13 days but can range from 5 to 21 days. The invasion period is characterized by back pain, myalgia, intense headache, fever, lymphadenopathy, and intense asthenia. The disease monkeypox is an illness characterized by vesicle and pustule formation. The skin eruption begins within 1–3 days of fever. The rashes are observed mainly on face (95%), palms of the hands and soles of the feet (75%), oral mucous membranes (70%), genitalia (30%), and conjunctivae (20%). The symptoms last from 2 to 4 weeks. Monkeypox is generally a self-limiting disease, but may be severe in children, pregnant women or immunosuppressed individuals related to the health condition of patients and nature of complications. Underlying immune deficiencies may lead to worse outcomes. The complications may include secondary infections, bronchopneumonia, sepsis, encephalitis, and loss of vision. In people who comes in contact with the virus and have not been vaccinated against Smallpox an attack rate (secondary) of around 10% has been noticed. The case fatality rate (CFR) varied from 1 to 11%. Scar formation and other consequences are frequent in people who survive [3]. West African clade of monkeypox virus causes less severe disease with 3.6% CFR in humans as compared to the Congo Basin clade with 10.6% CFR.

This virus is believed most likely to transmit from rodents to people. In spite of the re-emerging nature of the monkeypox disease in human the natural animal reservoir for this virus has not been identified yet and thus the behaviours of the human that augment transmission to human from animal initially are not confirmed. Transmission of the virus from one animal to other can take place and subsequent infection of the human is possible. Such incidences have been reported from United States (US) wherein infection of people including children took place from prairie dogs. These dogs were found to pick up infection from rodents which were shipped from Ghana to the US [11]. However, further studies are highly recommended to identify the exact reservoir and to know more about the virus circulation and its evolving epidemiology [2, 12,13]. The changing epidemiology and re-emergence of monkeypox in Africa also demands One Health strategies to be emphasized to counter this important zoonotic disease [14].

Human-to-human transmission occurs among people in close physical contact with symptomatic monkeypox cases via body fluids (saliva from coughing, respiratory secretions and droplets), skin lesions of the infected person and from contaminated objects such as clothing, bedding or utensils [1,15]. Eating inadequately cooked animal products and meat of infected animals may be a possible risk factor. There are very limited studies to understand the epidemiology, sources of infection, and transmission patterns of such recently identified monkeypox cases, and the virus is spreading continuously. Reported cases have no

<https://doi.org/10.1016/j.ijso.2022.106705>

Received 23 May 2022; Accepted 8 June 2022

Available online 11 June 2022

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recognized travel links of spread to non-endemic areas. It is important to discuss why most of the cases include men (most are gay) aged 20–50 and have sex with men, seeking care in primary care and sexual health clinics. According to ECDC, the recent unexpected cases among men who have sex with men have involved lesions in their genital area [16]. But the sexual transmission of monkeypox virus is not reported yet. Hence, it is suggested that the current clusters may be due to close contact. As per MacIntyre, the monkeypox virus may be coincidentally introduced into this community and has circulated within sexual networks [1].

The antibody and antigen detection methods do not provide monkeypox-specific confirmation as orthopoxviruses are serologically cross-reactive, therefore real-time PCR and sequencing are needed for confirming the virus. The presently PCR confirmed cases of monkeypox have been identified as to be of West African clade. Genome sequencing from a confirmed case in Portugal reflected a close match of the currently identified monkeypox virus to the exported cases from Nigeria to the UK, Israel and Singapore in 2018 and 2019 [2].

Smallpox vaccine has been proven largely protective (85% effective) in preventing the spread of the monkeypox virus. The prior smallpox vaccination may result in milder illness. After eradication of smallpox disease and cessation of smallpox vaccination campaigns, persons younger than 40–50 years are more susceptible to monkeypox [5,11]. As the original smallpox vaccines are no longer available, a newer vaccine based on a modified attenuated vaccinia virus (Ankara strain) was approved in 2019 for prevention of monkeypox. This is a two-dose vaccine with limited availability. Some countries (the UK and Spain) are now offering the vaccine to the infected individuals to reduce the spread of the virus [17]. It is interesting to note that IMVAMUNE (a third generation vaccine against smallpox) has also been tried in healthcare workers who are prone to contract monkeypox in the Republic of Congo [18]. Licensing of this vaccine has been done by the Food and Drug Administration (FDA) to prevent monkeypox in people of age 18 years and more. It is quiet important to note that IMVAMUNE can be used in patients suffering from AIDS as well as atopic dermatitis which is not the case with another vaccine ACAM2000. However, efficacy of such vaccine in endemic regions is yet to be determined [18–20]. Above all, subsidy is essential partially for achieving greater coverage of vaccination especially in case of general practitioners at various health centres as is evident by a cross-sectional study conducted in Indonesia [21].

The drug brincidofovir (a drug against smallpox) has been investigated for its efficacy in monkeypox virus animal model. *In vivo* testing of this drug has not been done against smallpox. Thus it is critical to understand the protective nature of this drug at the phase of an outbreak of smallpox by conducting studies with the related monkeypox virus [22]. ST-246 is an antiviral compound which is found to have inhibitory action against seven strains of monkeypox virus [23]. The antiviral tecovirimat which was developed for smallpox treatment has now been licensed for monkeypox treatment in 2022. Another antiviral cidofovir can also be used to control the outbreak [24]. It requires a special mention here that when the drugs brincidofovir and cidofovir are compared *in vitro*, the former has greater toxic effects but better activity against monkeypox virus. The selective index of brincidofovir is also higher [20]. However, it is suggested to monitor their use in a clinical research context with prospective data collection. The secondary bacterial infections may also be treated as indicated.

Enhancing active surveillance and rapid identification of new cases of monkeypox is critical. In monkeypox outbreak, close contact with infected persons is the most significant risk factor. Making awareness programs to educating the risk factors and to reduce exposure to the virus is the main prevention strategy for monkeypox. The suspected monkeypox patients must be isolated in a negative pressure room and the staffs must be encouraged to wear appropriate personal protective equipments each time near the suspected cases [15]. Multidisciplinary attempts (led locally) in close association with capacity building and training are required in a coordinated manner for advanced

preparedness from the public health point of view. Such attempts are also essential for putting into order proactive surveillance actions and research activities on priority basis [4,5]. It is also suggested to maintain adequate nutritional status of the patients.

It is still unknown much that the monkeypox virus causing the current outbreaks is to what level similar and linked to the viral strain predominantly found in western Africa as well as its means of rapid transmission are being explored. It is a big challenge for the virologist to find answers about sudden rise in monkeypox cases posing global threats, and is there any mutation(s) in viral genome that plays a role to allow this monkeypox virus to transmit more readily than those of the past western African origin. Of note, monkeypox virus and SARS-CoV-2 are very different but both viruses cause flu-like symptoms initially. Monkeypox typically begins with flu-like illness followed by swelling of the lymph nodes and rash on the face and body. Monkeypox virus is a relatively large DNA virus than RNA virus. The sudden mutation of the monkeypox virus in human transmission is unlikely as DNA viruses are better at detecting and repairing mutations. SARS-CoV-2 is a RNA virus so its variants are continuously emerging and have eluded immunity from vaccination and prior infection. But in case of monkeypox, the immunity of the people from vaccination and prior infection is yet to be determined. As like SARS-CoV-2, if somehow monkeypox virus could gain to spread asymptotically then it would be very troubling to track it. Furthermore, explorative investigations and research studies are needed to identify the exact reservoir(s) of monkeypox virus, how this virus maintains circulation in nature and the reasons behind the current rising cases in several countries.

The recent spread of monkeypox in multiple countries under lack of any travel history to an endemic country is atypical and outbreaks beyond Africa highlight its global relevance. Considering the rapid spread of monkeypox virus in few countries as well as likely potential threats of more cases being identified with further spread to other non-endemic countries could pose high global public health concerns. Therefore, surveillance programs in non-endemic areas/countries need to be expanded quickly along with studying extensive and comprehensive monkeypox case findings, contact tracing, laboratory investigations, clinical management and isolation of patients while rendering appropriate supportive healthcare to limit further transmission of this virus. Higher attention is warranted towards high-risk patient groups, and potential risks of nosocomial transmission of monkeypox [2–4]. Genomic sequencing facilities are to be strengthened for determining the involvement of monkeypox virus clade(s). Besides these, appropriate and timely awareness campaigns for populations at risks, readiness and proactive response efforts, technical guidance for urgent recommended action plans are the priority needs to tackle the spread of monkeypox in the current times while facing the ongoing COVID-19 pandemic [2]. After smallpox's eradication many a years back, smallpox vaccination has been stopped that also kept monkeypox at bay, the proportion of population having weakened or no immunity to these poxviruses has increased [2,11]. Also, there is very less immunity to monkeypox virus in younger populations living in non-endemic areas as the virus has not been reported earlier there. Specifically to mention that though one vaccine (MVA-BN) and one specific drug (tecovirimat) have been approved in 2019 and 2022, respectively for counteracting monkeypox, however both of these are yet not widely available. Vaccination for monkeypox, where accessible, is being deployed for managing people with close contacts, especially the healthcare workers [2].

All the countries need to be on alert for identifying monkeypox cases immediately which would help in checking further spread of this virus. Especially, protecting frontline healthcare workers and laboratory staff is necessary by quick detection, identification and isolation of monkeypox cases so as to prevent further secondary cases and design effective management practices to be adopted to control the current outbreaks. It is worth to mention that though the exact modes of transmission of the current monkeypox virus outbreak are still under

investigation, however the general precautionary strategies against SARS-CoV-2 amid the ongoing COVID-19 pandemic could also largely aid in limiting the transmission and spread of monkeypox virus. An up-to-date comprehensive, reliable and longer-term research planning is urgently required to understand monkeypox virus completely while addressing the research gaps and unresolved questions for disease's emergence, epidemiology, and ecology as well as enhance surveillance capacities, design appropriate prevention, preparedness and immediate response activities. Priority needs to be given to gain better understanding of the genomic evolution, changing epidemiology, ecologic niche modelling and find out animal reservoir(s) for monkeypox virus, implement One Health concept more strongly and widely, formulate evidence-based immediate responses and best management/control strategies to tackle monkeypox virus outbreaks efficiently, which will altogether aid in ultimately reducing its human infections.

### Ethical approval

This article does not require any human/animal subjects to acquire such approval.

### Sources of funding

No funding received.

### Author contribution

RKM: Conceptualization, made the first draft; HST, AKS, SC, DC, CC: updated, reviewed; KD: Conceptualization, writing – review & editing. All authors critically reviewed and approved the final version of the manuscript before submission.

### Research registration Unique Identifying number (UIN)

Name of the registry: NA.

Unique Identifying number or registration ID: NA.

Hyperlink to your specific registration (must be publicly accessible and will be checked): NA.

### Guarantor

All authors.

### Provenance and peer review

Not commissioned, internally peer-reviewed.

### Declaration of competing interest

No conflicts to declare.

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