

Why Should RNA Viruses Have All the Fun – Monkeypox, a Close Relative of Smallpox and a DNA Virus

Looking at the potential of the two kinds of viruses, the RNA and DNA viruses, to cause epidemics and pandemics, the RNA viruses clearly stand out.^[1] Some of the prominent RNA viruses in this category are *Orthomyxoviruses* (Influenza and H1N1 pandemics), *Coronaviruses* (severe acute respiratory syndrome, Middle East respiratory syndrome, and COVID-19 pandemics), *Flaviviruses* (Japanese encephalitis, Dengue, yellow fever, West Nile fever), *Filoviruses* (Ebola and Marburg), *Paramyxoviruses* (Nipah), and many more.^[2] The DNA viruses have been present in and coevolved with humans for long periods and therefore rarely cause outbreaks and pandemics.^[2] Most RNA viruses are zoonotic and many of them have recent zoonotic evolution making humans more susceptible to outbreaks from them.^[1,2] Ever since the eradication of the dreaded DNA virus Variola major that caused smallpox (SPX), in 1980, none of the other DNA viruses have got much attention of public health professionals, international media, and public for being a cause of concern for global health security.^[3]

However, this all changed in the past few weeks with the reemergence of a DNA virus which is a very close relative of SPX, and a member of the pox family, i.e., Monkeypox (MPX).^[3] While this presents a coherent picture, there is new evidence that MPX may have been in Europe before May 4.^[4] Over 400 confirmed or suspected cases of MPX have been reported from 20 nonendemic countries in just 2 weeks in May 2022, none of which have direct links to the endemic regions in Africa.^[5-7] Although the cases and outbreaks have been reported with an increasing frequency in the past few decades from many parts of the world, most of these could be linked to their origin in either West Africa or Central Africa.^[3,5] What is different with the current outbreak is that these fresh cases have been reported from the United States (US), United Kingdom (UK), Spain, Portugal, Italy, Belgium, Sweden, France, Canada, Australia, Germany, and the Netherlands in a pattern that does not match past outbreaks, and no clear links have been established with Africa or infected exotic pets as was the case in past outbreaks.^[8,9] The origins of this outbreak may be in a single confirmed case in a British resident who traveled to Nigeria where small MPX outbreaks are occurring.^[4] The rapidity of the spread is surprising in view of both what is known about previous outbreaks spreading in Africa and other locations. For example, during an outbreak in the US in 2003, all individuals who were infected were traced to contact with prairie dogs infected by imported animals from Africa.^[10] In 2018, the UK outbreak started with a traveler from Nigeria who infected only two other individuals.^[4]

On an average, a few thousand cases of MPX are seen every year in Western and Central Africa but this recent modern world outbreak assumes significance because the number of cases reported in just 1 week has surpassed the total number of cases reported in these areas in the past 40 years and these numbers are expected to increase in the coming days.^[3,11] Furthermore, another major concern is the possibility of permanent establishment of MPX in the natural reservoirs making it endemic in the new areas outside of Africa. MPX unlike SPX is a zoonotic disease and can establish itself in a number of rodent and nonhuman primate species easily available worldwide, making MPX a potential threat to the world.^[12]

The ongoing events around this DNA virus MPX makes us review the potential future possibilities, threats, and outcomes associated with this virus. MPX and SPX have been affecting humans for thousands of years since they settled for agriculture, producing somewhat similar clinical manifestations.^[12] To understand the reasons behind reemergence of MPX after 40 years of SPX eradication, we must study the similarities and differences between the two close relatives, i.e., MPX and SPX [Table 1].

Since SPX and MPX competed with each other for the same host, i.e., humans, only one with a higher R_0 could be the winner. In this case, it was SPX till 1980 and during the SPX era, there were no reported outbreaks of MPX simply because SPX infection gave humans protection toward all other related poxviruses.^[13] Eradication of SPX in 1980 was possible because humans were the only reservoir for the SPX virus, we had an effective vaccine, and there were no subclinical or latent cases that could harbor this virus for long.^[13]

Now, 42 years down the line, when the residual orthopoxvirus immunity provided by SPX vaccination has fallen to 10%–25% and natural infections with orthopoxviruses are uncommon to provide natural immunity to unvaccinated humans, we have again become susceptible to MPX and according to the mathematical models, the R_0 of MPX can now reach anywhere between 1.1 and 2.4.^[13] This R_0 would be sufficient for independent human-to-human transmission to establish MPX outside of Africa. The zoonotic nature of MPX will be its advantage over SPX that infected only humans. We have already seen MPX outbreaks from infected imported prairie dogs to humans in 2003 in the US when MPX was confirmed in 35 cases and suspected in additional 36 cases.^[10]

Other factors in Africa that have contributed to the resurgence of MPX other than the waning herd immunity include the

Table 1: Comparing various features of Smallpox and Monkeypox

	Smallpox^[12,13]	Monkeypox^[12,13]
Family, genus	<i>Poxviridae, Orthopoxvirus</i>	<i>Poxviridae, Orthopoxvirus</i>
Species	<i>Variola virus</i>	<i>Monkeypox virus</i>
Reservoir	Only humans	Zoonotic (Rodents, anteaters, prairie dogs, opossums, and several nonhuman primates)
Clades	Variola major (30% mortality) Variola minor (1% mortality)	Central African (11% mortality) West African (1% mortality)
Reproduction number R_0	3.5-6	1-2.5
Clinical features	Fever, vesicular rash, headache, hemorrhages	Fever, vesicular rash, headache, lymphadenopathy
Current status	Eradicated	Endemic in central and West Africa, Outbreak in Developed countries (May 2022)
Vaccines	Available but not given to population since 1980	Available, the smallpox vaccine is protective

climate change, rainforest exploitation, geopolitical and armed, and highly mobile populations.^[3] Factors associated with the current or future outbreaks can vary and interestingly, the latest cases worldwide are reported mainly in men who have sex with men.^[9] There are multiple reasons why the MPX outbreak might be spreading rapidly, including a super spreader event associated with global travelers, and changes in the properties of the virus due to mutating, however, recent sequencing suggests it has not changed significantly from the 2018 UK outbreak.^[7] Although MPX is not known to be a sexually transmitted disease, it is likely to have been passed on through close contact with infected people. The main mode of transmission of MPX is respiratory droplets during close contact (face to face) and exposure to the bodily fluids of an infected person.^[9] The typical symptoms of MPX include fever, headache, body aches, and lymphadenopathy. Lymphadenopathy is typical for MPX and was not seen prominently with SPX.^[9] Fever is soon followed by a rash that appears first in the oropharynx and face then spreading to the trunk and limbs in a centrifugal pattern. The rash goes through different stages starting from macules or papules to vesicles and finally pustules that turn into scabs and fall off.^[9]

Both, SPX and MPX have typical clinical features that make their identification easy in the infected people. Such people can then be isolated in negative pressure rooms and cared for wearing protective equipment that includes N-95 masks, eye covers, and impervious gowns. The virus is unlikely to cause a major economic impact at the moment when compared to the recent COVID-19 pandemic simply because the vaccines are available, disease manifestations can be easily picked, and cases can be isolated. Furthermore, using the ring vaccination, where public health professionals vaccinate all people surrounding the index cases can be employed to curtail the spread of MPX just as was the case with SPX. Still, the dangers associated with zoonotic potential of MPX and waning immunity to pox viruses may necessitate adoption of mass vaccination programs in future, especially in areas where MPX becomes endemic.

Effective public health surveillance and outbreak response is a priority during public health emergencies in affected

populations. Due to the disruption of health and other social services during the emergencies, the routine integrated disease surveillance and response (IDSR) system must be enhanced to meet the public health surveillance and outbreak response needs in humanitarian contexts. MPX surveillance is crucial from public health perspective and calls for the identification of patients according to time place and person. Detailed case investigation and specimen collection identification of primary and secondary cases is the need of the hour.

Some notable features of the current MPX outbreak are that its sequenced viral genome from Belgium, Germany, Portugal, France, and the US closely resembles that of the strain endemic in Western Africa.^[7] The West African clade of MPX has low mortality of 1% [Table 1] compared to the Central African Clade with around 11% mortality.^[7]

To conclude, the current MPX outbreak is one rare example of a DNA virus gaining international attention, just because it has a zoonotic potential. Most other DNA viruses lack this special feature seen only with RNA viruses, most of which are zoonotic. MPX can assume significance in poor nations where public health infrastructure is not strong enough to contain the virus and prevent it from establishing itself in local animal reservoirs. This also means that more funding and research is needed to understand the genomics, changing genetic structure, surveillance, and control of MPX.

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DOI:
10.4103/jgid.jgid_104_22

How to cite this article: Thakur S, Kelkar D, Garg S, Raina SK, Lateef F, Gilada I, *et al.* Why should RNA viruses have all the fun – Monkeypox, a close relative of smallpox and a DNA virus. *J Global Infect Dis* 2022;14:47-9.

Received: 03 June 2022

Revised: 16 June 2022

Accepted: 06 June 2022

Published: 29 June 2022