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Monkeypox Emergency: Urgent Questions and Perspectives

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## Voices

# Monkeypox emergency: Urgent questions and perspectives

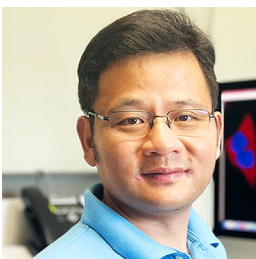
Amidst the COVID-19 pandemic, we now face another public health emergency in the form of monkeypox virus. As of August 1, the Centers for Disease Control and Prevention report over 23,000 cases in 80 countries. An inclusive and global collaborative effort to understand the biology, evolution, and spread of the virus as well as commitment to vaccine equity will be critical toward containing this outbreak. We share the voices of leading experts in this space on what they see as the most pressing questions and directions for the community.



**Stefan Rothenburg**  
University of California Davis, USA

### Poxvirus evolution

In medical school, I told my students that they will likely see poxvirus outbreaks in their careers. However, the magnitude and rapid spread of this global outbreak is unexpected and deeply concerning. Entry of poxviruses into cells is independent of host-species-specific receptors, and poxviruses thus have the potential to infect many different species. Sequence data from variola virus, which caused human smallpox, indicate that poxviruses have relatively low mutation rates when they are transmitted within one species. However, poxviruses have genomes that are less size constrained than most other viruses. This flexibility can help them to adapt to new hosts. Adaptive genomic changes include gene duplications, gene loss, recombination with closely or distantly related viruses, and horizontal gene transfer from their hosts to gain new genes. Moreover, low-frequency single-nucleotide polymorphisms might be beneficial in the new host and become more abundant. This might explain the unexpected high number of “mutations” found in the viruses of the current outbreak. One key question is how these variations affect monkeypox virus (MPXV) transmissibility and virulence. Because of the rapid increase in MPXV cases, there is a high chance that the virus is going to stay with us for a long time and potentially establish itself in pets and wildlife worldwide. An expanded virus reservoir greatly increases the risk that more adaptive mutations will arise, for example, after recombination with other poxviruses. We urgently need a coordinated and well-funded surveillance of poxvirus infections to be able to detect and quickly react to new variants of concern.



**Zhilong Yang**  
Texas A&M University, USA

### Comprehending the fundamental virology

Many questions surrounding the basic biology of MPXV demand answers to lay the foundations for developing effective strategies and tools to manage the disease. (1) Current understanding of MPXV in nature, particularly its animal reservoirs, transmission, and pathogenicity, is very inadequate. Much of the discourse has been based on limited data and assumed similarities to smallpox. (2) Like other poxviruses, MPXV virion and its replication are exceedingly complex. High-resolution virion structures are lacking, and some steps of the replication cycle are still elusive. (3) MPXV encodes ~190 proteins to build viral particles and modulate numerous host processes. The interactions between viral proteins and host functions shape infection outcomes, including pathogenicity, host range, transmission efficiency, and evolution. We need to understand the functions of these proteins and their interactions with hosts. Studies of homologous proteins in other poxviruses like vaccinia virus can facilitate dissecting the functions of MPXV proteins. As a zoonotic pathogen, MPXV will likely stay with us in the foreseeable future due to its broad host range with multiple animal reservoirs, even if the current global outbreak is contained. Future outbreaks are expected due to waning population immunity to smallpox, increased human-animal contacts, and global travels. It is critical to study the fundamentals of MPXV at the molecular, cellular, tissue, organismal, community, and ecosystem levels under the One Health concept to address the long-term challenges. Comparative studies of different poxviruses will provide further insights.



**Pip Beard**  
Pirbright Institute, UK

### Monkeypox from the veterinary perspective

The extended chains of human-to-human transmission of MPXV that have been reported in previously non-endemic countries have led to a fundamental shift in our understanding of monkeypox. It is a real “rewrite the textbooks” situation. In the veterinary field, we have a similar unprecedented poxvirus event in cattle caused by lumpy skin disease virus (LSDV). In the past decade, this poxvirus has spread from Africa into the Middle East, Europe, and throughout Asia, causing severe illness and the death of thousands of cattle. Who would ever have thought that we would be facing two substantial outbreaks of poxviral disease? Poxviruses are well and truly back in the spotlight.

Variola virus, the causative agent of smallpox, is a highly host-restricted virus that infects and causes disease only in humans. This characteristic was one of the key factors leading to the successful global eradication of smallpox. MPXV is different. It is from the same genus as variola virus but is not so tightly host restricted and employs wild rodents as primary reservoirs with (until recently) occasional spillover leading to cases of MPXV in humans. A very similar situation exists with another closely related poxvirus, cowpox virus, which uses small rodents such as voles as reservoirs with sporadic cases in cats, pet rodents, and humans. The establishment of a reservoir of MPXV in a wild rodent population in a previously non-endemic region is now a distinct possibility and would make control and eradication, as achieved with variola virus, much more challenging. An assessment of potential routes for zoonotic and reverse-zoonotic transmission of MPXV is a priority, using a clear One Health framework.



**Sara L. Sawyer**  
University of Colorado Boulder, USA

### Comparing HIV/AIDS and monkeypox

Since the 1980s, HIV has killed or chronically infected around 75 million people—approximately 1 out of every 100 persons globally. Could MPXV cause a pandemic like this? Here, I want to review key differences between the two viruses that make MPXV less alarming than HIV. First, when the 2022 global MPXV outbreak began, we already had vaccines that probably protect against infection. In contrast, 40 years into the HIV/AIDS pandemic, we still have no vaccines. Second, most people recover from infection with the current outbreak strain of MPXV, which causes acute infection that typically resolves. In contrast, essentially nobody recovers from HIV, which causes a [life-long chronic infection](#). Third, the virus strain causing the current MPXV outbreak has a low case fatality rate. In contrast, HIV/AIDS is basically fatal for everyone unless they receive life-long antiretroviral drug treatment. (On this last point, it should be noted that other MPXV strains in Africa have far higher case fatality rates; also, the current strain has the possibility of mutating into deadlier forms.) Let’s hope that MPXV pathogenicity stays low in the global outbreak and that the existing vaccines offer safe and durable protection that also stands up to viral variants. These would be important ways that the MPXV outbreak is different from HIV/AIDS. Lastly, let’s not forget about HIV/AIDS, for which vaccines are still desperately needed.



**Boghuma Titanji**  
Emory University, USA

### Neglect comes at a cost

For over five decades, MPXV disease primarily affected poor people in remote parts of west and central Africa. Despite increasing numbers of cases through the years and the threat of larger outbreaks, it struggled to garner meaningful international attention. Funding for research and much needed surveillance were sorely lacking. In recent months, we have seen a radical shift in the attention given to MPXV as a direct result of a global outbreak that has affected wealthy countries in North America and Europe. The sense of urgency is palpable but tainted by the hypocrisy of the 50 years of neglect that preceded the current situation. This pattern is reminiscent of other emerging diseases like Ebola virus disease, also grossly neglected, prior to the large outbreak in West Africa in 2014–2016 and importation of cases to western countries. Now that MPXV has the attention of the global community, the biggest test is yet to come. Will this finally be the moment where true solidarity in a global public health response becomes reality? Or will we again see the mistakes of the past repeated and inequities amplified in a failed global response? We have the opportunity to get things right this time around and prevent another zoonotic virus from establishing itself in the human population, but the

response must be centered on equity and giving everyone a seat at the table, especially African countries who have borne the brunt of the virus for much longer than newly affected countries. Neglecting MPXV in Africa led to it becoming an emerging pandemic; no one should be left behind in the global response needed to confront this threat.



**Gregg Gonsalves**  
Yale University, USA

### Containment or persistence: The choice is ours

As a gay man who came of age in the early years of the AIDS epidemic, the emergence, 40 years later, of another virus among men who have sex with men (MSM), filled me with a sense of dread. Would the world with the experience of HIV/AIDS (and COVID-19) move swiftly to contain this new outbreak of a disease once mostly limited to an endemic range in west and central Africa? After 2 and a half months, with known virus and effective vaccines, I would have expected us to be well on our way to containment of MPXV among MSM. Instead, cases have continued to mount with now over 20,000 cases in over 70 countries—a wide and rapid spread in only a few short weeks. How did we get here? First, the outbreak began with close, physical contact at large, international social gatherings, which functioned as superspreader events. These also involved anonymous sexual encounters, making the tracing of contacts of known cases difficult to do. Second, in some countries, the scale-up of testing and [case identification has been slow and hampered by bureaucracy](#). Third, the key vaccine to prevent infection—[Bavarian Nordic's modified vaccinia Ankara JYNNEOS—is in short worldwide supply](#), which means vaccination campaigns to immunize MSM cannot be launched at scale. At this moment, we stand at a crossroads, with containment or persistence of MPVX among MSM our two divergent futures. Unless the global public health community significantly ramps up its efforts right now, MPXV may be with us for many years to come around the world.



**Jason Kindrachuk**  
University of Manitoba, Canada

### The best defense is a good offense

As the COVID-19 pandemic has dominated lives and livelihoods for more than 2 years, there has been ample discussion on pandemic prediction—what will be the next pathogen we face, and where will it emerge from? However, we must appreciate that emerging threats do not have to be novel to impart global health and economic impacts. In 1970, as we entered the last decade of the historic fight against smallpox, the first case of human MPXV was identified in the Democratic Republic of Congo. More than 50 years later, repeated concerns regarding MPXV as a global health threat have come to fruition.

The reality of the current global MPXV outbreak is that while the breadth and presentation of cases was unpredictable, the warnings that this could happen have resonated for years. As a global community, we must appreciate that there is an urgent need to get transmission of MPXV contained across the globe. However, we must also appreciate the continuing need for sustained global investment in surveillance, preparedness, and response in endemic and vulnerable regions. Additionally, we need to re-emphasize the importance of engagement and collaboration with regional experts from endemic regions—those who have been embroiled in this fight since 1970.

Lastly, this is also a moment to reflect on the complex nature of emerging infectious diseases and our need to counter this with rapid engagement of international partners. An example of this is the expedient [release of clinical and infection prevention control guidance documentation on MPXV](#) as well as [international consultation on a global core protocol for evaluation of therapeutics](#). The old adage of “the best defense is a good offense” is apt in this regard. Prepare for the unpredictable, and prepare globally.

### DECLARATION OF INTERESTS

S.L.S. is a founder of Darwin Biosciences and a member of its scientific advisory board. She serves as a consultant for the MITRE Corp. and as a senior editor at the journal *eLife*. She is a member of the Planning Committee for Countering Zoonotic Spillover of High Consequence Pathogens, sponsored by the Academies of Sciences, Engineering, and Medicine. B.T. has received consulting fees for the non-profit organization CRITICA for work unrelated to the present publication.