EDITORIAL

Mpox, smallpox and the increasing threat of orthopoxvirus epidemics.

C Raina MacIntyre[1]

[1]Kirby Institute, University of New South Wales, Sydney, Australia

Abstract

An epidemic of clade I mpox in the Democratic Republic of Congo, low population immunity to orthopoxviruses and advances in synthetic biology should be the triggers to raise our level of preparedness for resurgent orthopoxvirus epidemics.

Keywords

Smallpox, Mpox, orthopoxvirus, Epidemic, pandemic

We should be on high alert for orthopoxvirus epidemics because of large, ongoing epidemics of mpox in the Democratic Republic of Congo (DRC). Mpox has been resurgent in the African continent in countries like Nigeria and DRC since 2017, where the infection is endemic in animals and can be zoonotic or human-to-human transmitted. It remained a low priority until the 2022 epidemic which affected non-endemic, high-income countries in Europe and the Americas. The latter epidemic appeared to be mostly spread between men who have sex with men, with origins in the 2017 clade II epidemic in Nigeria. (1) This showed continuous and rapid evolution, which was surprising, as orthopoxviruses are stable DNA viruses. (2) The 2022 strain which caused the epidemic in non-endemic countries is now classified as clade IIb. (3) If the virus becomes established in animal hosts in Europe, the Americas and other non-endemic areas, it could become endemic, posing a permanent risk of zoonotic outbreaks in a wider geographic area. Clade II, however, has a lower case fatality rate than clade I.

The most concerning situation is the clade I Mpox epidemic in Kamituga, DRC. From January to November 2023 the World Health Organization reported 12,569 suspected mpox cases in DRC, with a 4.6% case fatality rate, (4) with 70% of the cases and 88% of deaths are in children. (5) Less than 10% of these were tested by PCR, due to low diagnostic capacity in DRC. The predominance of children in the DRC epidemic suggests transmission may be respiratory. In fact, smallpox and mpox are respiratory viruses, and mpox has been identified in ambient air. (6) Variola was highly airborne, with the potential to transmit over long distances. (7) If the more pathogenic clade I mpox becomes highly transmissible between humans, it may pose a greater pandemic threat than clade IIb. A recent study of an outbreak in Kamituga, DRC near the border with Rwanda reports a new mutation of clade 1 Mpox, termed clade 1b, which may pose a pandemic threat as it is more readily transmissible between humans. (8) The lack of diagnostic capacity and the need for heightened surveillance in DRC is a dilemma. However, the nature of the rash makes a clinical case definition and a syndromic surveillance system a reasonable alternative when laboratory diagnosis cannot be made.

In low-income countries with low diagnostic capacity, use of open-source intelligence may also help in detecting early warnings by identifying outbreaks of rash and fever. (9) Our early warning system, EPIWATCH®, (10) detected a report from Jayapura in Indonesia of an outbreak of an illness featuring a rash which looks like it could be an orthopoxvirus. Local news agencies or social media often report outbreaks before health authorities are aware of them, making open-source intelligence (OSINT) a valuable early warning tool. (11) OSINT can prompt earlier investigation and diagnostics. The Indonesian report mentions chickenpox (varicella) and mpox, and the outbreak has apparently been diagnosed as varicella. The rash of varicella is typically centripetal (affecting the trunk more than the limbs), whilst the rash of mpox or smallpox is centrifugal, affecting hands, feet, face and limbs more than the trunk. In addition, the lesions in orthopoxvirus infections are typically at the same stage of development, whilst in varicella, they are at different stages of development. A further diagnostic problem is that mpox and varicella coinfection is surprisingly common. In Brazil and Nigeria, coinfection rates of 20-28% have been reported (12, 13). This poses a challenge for surveillance and diagnostics, as epidemics of mpox may be masked by varicella, which is easier to test for. Therefore testing for mpox may not be done at all once a diagnosis of varicella is made. The outbreak in Indonesia is allegedly not an orthopoxvirus, but the threat of re-emergence of orthopoxviruses remains high.

In the era of smallpox, there was widespread exposure to variola and mass vaccination, but vaccination against smallpox ceased in the 1970s and earlier in most countries. Smallpox vaccines are protective against other orthopoxvirus infections such as mpox. (14, 15) However, 44 years after the eradication of smallpox was declared in 1980, waning vaccine immunity in older people, as well as accumulation of younger people who have never been vaccinated, means humans are now immunologically more susceptible to orthopoxvirus infections. (16, 17) Mpox began to re-emerge in Nigeria in 2017. We calculated that population immunity had waned to a critical threshold of 2%, and this corresponds with the large epidemics seen thereafter. (18) Emergence of other novel orthopoxviruses such as Alaskapox, which emerged 9 years ago,(19) is also possible given this immunological landscape.

Smallpox can theoretically re-emerge through synthetic biology. The methods for synthesising an orthopoxvirus were published in an open-access journal in 2018. (20) The risk of smallpox is real, due to reducing costs (21) and greater access to such technology. (22) If an emerging orthopoxvirus such as clade 1 mpox has an R0 of >1, it has epidemic and therefore pandemic potential. True epidemic infections can grow exponentially, (23) and we previously showed that even one week of delay makes a difference to epidemic size for smallpox. (24, 25) Exponential growth is what causes sudden, severe perturbations in society and crashes health systems, because cases rise from a few to large numbers within a very short time, such as we saw during the COVID-19 pandemic in 2020. A smallpox pandemic could cause the same, as we showed with a model of health system impacts. (24) In a smallpox pandemic simulation, we also identified key, modifiable points of delay which influence epidemic growth. (26, 27) Preparedness should plan for reducing these delays. This includes early diagnosis, having a pre-vaccinated cohort of first responders, stockpiling of drugs and vaccines, and rapid deployment of vaccines. (26) Right now, the situation in DRC is the most concerning globally, and we must keep our levels of preparedness high.

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