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Human mpox: global trends, molecular epidemiology and options for vaccination

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ABSTRACT

The eradication of smallpox and the cessation of vaccination have led to the growth of the susceptible human population to poxviruses. This has led to the increasing detection of zoonotic orthopoxviruses. Among those viruses, monkeypox virus (MPV) is the most commonly detected in Western and Central African regions. Since 2022, MPV is causing local transmission in newly affected countries all over the world. While the virus causing the current outbreak remains part of clade II (historically referred to as West African clade), it has a significant number of mutations as compared to other clade II sequences and is therefore referred to as clade IIb. It remains unclear whether those mutations may have caused a change in the virus phenotype. Vaccine effectiveness data show evidence of a high cross-protection of vaccines designed to prevent smallpox against mpox. These vaccines therefore represent a great opportunity to control human-to-human transmission, provided that their availability has short time-frames and that mistakes from the recent past (vaccine inequity) will not be reiterated.

KEYWORDS

Mpox; monkeypox; orthopoxvirus; molecular epidemiology; smallpox vaccination

Introduction and epidemiology of zoonotic orthopoxviruses

Poxviruses are ubiquitous viruses, able to infect a large range of hosts, which are part of the *Poxviridae* family. The latter is divided into two subfamilies: *Chordopoxvirinae*, which infect vertebrates, and *Entomopoxvirinae*, which infect invertebrates. The *Chordopoxvirinae* subfamily is further divided into 18 genera that are distinguishable by their serological reactions [1]. Four of these genera are known to cause human infections, typically following contact with animal species (i.e. zoonoses): orthopoxviruses, molluscipoxviruses, parapoxviruses, and yatapoxviruses [2].

The *orthopoxvirus* genus comprises the variola virus (VARV), the only member of the genus that is not a zoonosis, as it exclusively infects humans [3]. VARV is among the most studied viruses in the laboratory, because it has caused a deadly human disease, smallpox, for at least 3,000 years. The last human case of smallpox was reported in Somalia in 1977, and after intensive and global mass vaccination efforts, smallpox eradication was achieved in 1980. Vaccination against smallpox was achieved using a live vaccine containing another member of the *orthopoxvirus* genus, vaccinia virus (VACV), which is a zoonotic infection causing attenuated disease in humans and cross-protection against smallpox. Other orthopoxviruses circulating among humans include at least vaccinia virus and its sublineages [4], cowpox virus [5], camelpox virus [6,7], akhmeta virus [8], alaskapox virus [9], and monkeypox virus (MPV). Their common feature is that humans are accidental hosts and typically develop infection following occupational exposure (i.e. close contact with animals). Infections with these zoonotic orthopoxviruses are typically sporadic, can cause a few localized lesions – even though they can sometimes develop into systemic infections – and are associated with low morbidity and mortality [2].

Because orthopoxviruses share significant DNA sequence similarity, including key antigenic regions of the genome, all orthopoxvirus infections are considered to develop strong cross-protective immune responses [10,11]. Despite that many orthopoxviruses are named after the host in which they were first reported, their names do not necessarily represent the natural reservoir of the virus, and not much is known about the primary hosts and reservoirs of zoonotic orthopoxviruses in nature [3]. For the majority of zoonotic orthopoxviruses causing infections in humans, the suspected main reservoir is represented by wild rodent populations. Barriers to spill-over events include geographical, ecological, and behavioral characteristics, which differ for different orthopoxviruses. The long-lasting environmental stability of viral particles increases the likelihood of exposure [12]. The known host range also varies and is very broad for some of them (e.g. cowpox and vaccinia viruses). Such

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viruses often use receptors that are broadly present in mammals, therefore increasing the likelihood of successful infection in a new host. Orthopoxviruses possess a large set of genes that are immune-regulators, host range determinants, or virulence factors [3] and can encode for viral proteins that play a key role in determining host tropism, and interacting with host-mediated mechanisms, creating the right conditions for viral replication [13].

The eradication of smallpox in 1980, and the cessation of smallpox vaccination shortly after, means that current children and young adults under the age of 40 years are susceptible to orthopoxviruses, as no other orthopoxvirus has broadly circulated among humans since then. This has led to an increase in the reports of zoonotic orthopoxvirus infections in humans – an unintended consequence of smallpox eradication [14]. Those zoonotic orthopoxviruses include cowpox virus, endemic in Northern and Central Asia and Europe, for which cat- or rodent-to-human transmission is well recognized [15–20]; vaccinia virus-like strains, such as among others Cantagalo virus, found in some areas of Brazil [4], the buffalopox virus, found in Asia and the Middle East, both associated to outbreaks in dairy cattle with sporadic spillovers to humans via occupational exposure (e.g. milkers) [21,22]; camelpox virus, found in the Middle East and Central Asia and associated to outbreaks in camels with sporadic spillovers to camel handlers [23,24]; akhmeta virus, a poxvirus also found in rodents discovered in the Caucasian region and for which cow-to-human transmission has been reported [3,25]; and alaskapox virus, also thought to be a zoonotic orthopoxvirus but for which exposure causing human infection remains unclear [21,22]. All these viruses are known to have very low secondary attack rates, which typically translate in one or two generations of transmission, therefore causing self-limiting outbreaks. This notion has been increasingly challenged in recent years by MPV [26].

Historical overview of mpox

MPV is an orthopoxvirus endemic to central and western Africa. The virus was first identified in captive monkeys in 1958 [27] and from a human being in 1970 in the Democratic Republic of the Congo (DRC) [28]. Unlike the variola virus, which exclusively affected human hosts, MPV has a wide range of hosts, and rodents are a suspected reservoir [29].

The classic mpox presentation is a short febrile prodromal phase, which lasts 1–5 days and during which time patients may experience fever, headache, back pain, muscle aches, and lymphadenopathy. This is followed by a second phase which typically occurs after the fever subsides, with the appearance of skin and/or mucosal rash, which might include single or multiple lesions. Typically, the lesions progress through macules, papules, vesicles, and pustules, before crusting over and desquamating over a period of 1 to 4 weeks.

Initially considered only zoonotic, the virus has shown, especially in recent years, the potential for human-to-human transmission via close contact with lesions, body fluids, respiratory droplets, and contaminated materials [30].

Historically, mpox mainly affected the Congo Basin, where incidence rates started to increase in the 1980s [29,31] – an 8-times increase reported between 1981 and 1986, in part due to the implementation of active surveillance [29,32]. In 1996–97, an outbreak caused more than 400 cases, and hundreds of cases were reported in DRC in the 2000s [29,33,34]. Smaller outbreaks were also detected in the Republic of Congo and in South Sudan [35,36]. The relatively low number of cases reported in West African countries (Ivory Coast, Gabon, Liberia, Nigeria, and Sierra Leone) led to the initial hypothesis of limited capacity of human-to-human spread of the West African clade [31].

Comparison of active surveillance data in rural DRC from the 1980s until 2006–07 suggested a 20-fold increase in human monkeypox incidence [37]. Prior to the outbreak, DRC accounted for >90% of the overall number of suspected, probable and confirmed cases, most of which were not laboratory confirmed. After almost 40 years without reported cases, Nigeria experienced an outbreak in 2017 and since then it is the African country that has reported the most laboratory confirmed cases [38,39]. Outbreak investigations have revealed multiple introductions from wild animals and a single introduction along with human-to-human transmission in a prison facility [38]. The median age of cases in Nigeria falls in the 21–40 years old age group, and in DRC, the historical median age is 10 years old [37], which are both age groups that were not vaccinated against smallpox [40].

Thirty years after mass smallpox vaccination campaigns ceased, human monkeypox incidence has dramatically increased in rural DRC [37]. Similarly, Nigeria has also witnessed a dramatic increase in cases in 2017, which appears to have been driven by a combination of population growth, as well as accumulation of unvaccinated cohorts and decline in smallpox vaccine immunity [41]. Whether recent concomitant surges of Lassa fever in Western Africa [42] may have a common cause such as changes in the ecology of common animal reservoirs (i.e. wild rodents), remains undetermined.

Overview of the current outbreak

Prior to the current outbreak, MPV was detected outside Africa only in cases with travel history to Nigeria (Israel in 2018, Singapore in 2019, UK in 2018, 2019,

and 2021), and U.S.A. in 2021, or in cases resulting from contact with infected pet animals (prairie dogs) that acquired infection from Gambian pouched rats imported from Ghana to the U.S [43].

As of 12 July 2023, the current outbreak of mpox has affected 112 countries from all WHO regions with a total of 88,288 laboratory confirmed cases and 149 deaths [44]. Of the WHO reported cases with information on gender, 96% are males with a median age of 34 years (interquartile range 29–41). One per cent of cases are children or adolescents (0–17 years of age). Of note, among cases that reported sexual orientation, 87% self-identified themselves as gay, bisexual, and other men who have sex with men (GBMSM), and 48% of cases with known HIV status were positive [45]. The most common mode of transmission was sexual contact (69%). Among the cases who reported at least one symptom, 83% presented with any rash, 60% with fever, 52% with skin or mucosal lesions (excluding oral or genital lesions), 46% with genital rash, and 33% with headache [45]. It is important to note that most information from the current outbreak comes from clade IIb infections, with patients presenting with more mucosal lesions than previously described, often localized in the genital or perineal/perianal area.

The case–fatality ratio (CFR) for the current outbreak was 0.17% [45], which is significantly lower than previous CFR estimates for clade I and clade II (10% and 3–6%, respectively [26,38]). Except for Nigeria, where the increase in confirmed cases between 2021 and 2022 was >20-fold [46], there is little information on the epidemiology of the current outbreak in Central and other Western African countries, and it remains unclear whether these countries are experiencing a true surge in mpox cases since the current multi-country outbreak has started, or whether increase in detection is a result of increased awareness and testing followed by the declaration of a Public Health Emergency of International Concern from WHO on 23 July 2022 [47,48]. In Nigeria, the age distribution of mpox cases did not change between the period 2017–2021 and 2022–2023, with adults aged 21–40 being the most affected, with a majority being men, but higher proportion of women affected, as compared to the other countries experiencing the multi-country outbreak [46].

Molecular epidemiology of mpox

The MPXV genome comprises ~197,000 bp and includes hairpin terminals and more than 190 open read frames (ORFs) [40]. The highly conserved central coding region of the genome is flanked by variable ends. At least 90 ORFs are known to be essential for the virus [49,50].

The MPV genome terminal regions have repeated regions (ITR) with some paralogous genes. It is important to underlie the role of gene gain and loss in the virus evolutionary [51].

Additional non-essential ORFs play a role in the differences in tropism, immunomodulation, and host pathogenesis, with many ORFs still waiting to be functionally characterized [41].

There are two main variants of the virus, clade I and clade II, historically referred to as Congo basin (or Central African) clade and West African clade, respectively (Figure) [42,52]. Clade II, which appears

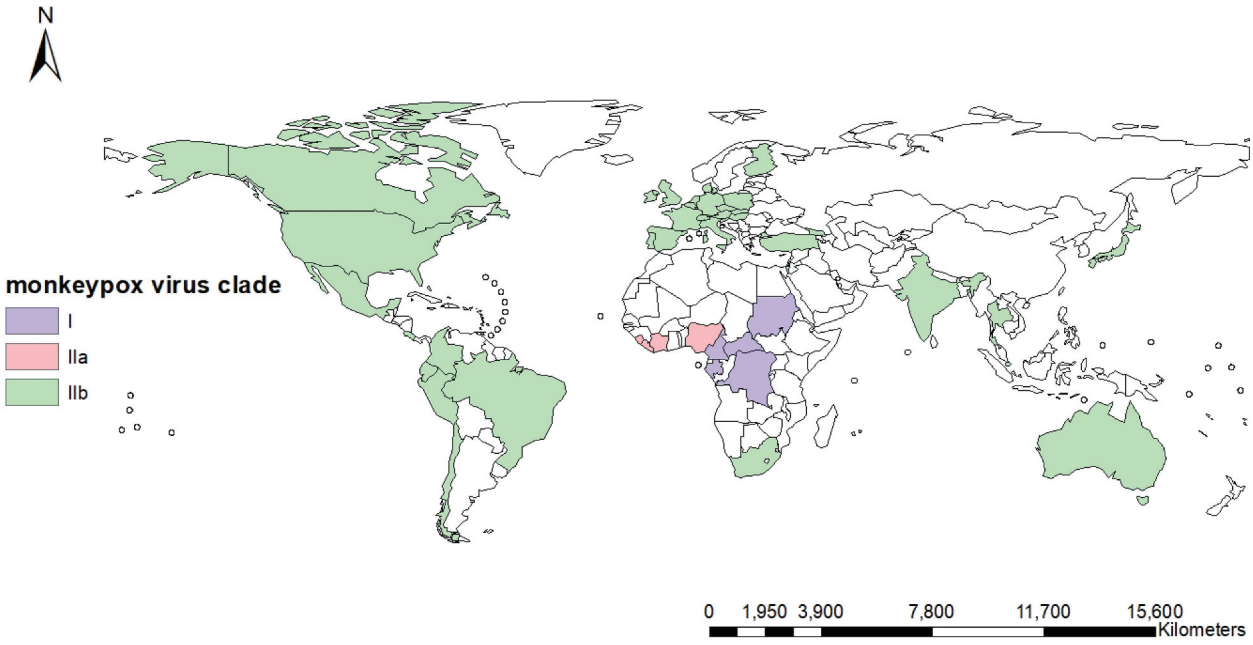

Figure 1. Map of the countries that detected monkeypox virus by clade. The map was generated using ArcGIS based on sequences that were deposited in publicly available databases such as GISAID and GenBank as of August 2022.

to cause less aggressive disease compared to clade I, has shown an epidemic resurgence in Nigeria since the year 2017 (Figure 1) [27,43].

The large outbreak of mpox reported in Europe so far appears to be due to a subclade of clade II (clade IIb, sometimes referred as clade 3) [44,45], as suggested by the analysis of virus genome from a patient diagnosed in Portugal at the beginning of the epidemic [46] and by the analysis of additional sequences of the 2022 outbreak [47]. Interestingly, all the outbreak strains sequenced so far for the current 2022 outbreak appear to cluster together, suggesting a single origin [46].

Phylogenomic analysis reveals differences among the genomes of outbreak strain due to the presence of SNPs also follow the same mutational bias [53]. However, recent studies pointed out the possible contribution of mechanisms intrinsic to the host, such as the apolipoprotein B mRNA-editing catalytic polypeptide-like 3 (APOBEC3) enzymes, host-enzymes with reported antiviral function, which could be driving this swift viral evolution favoring MPXV diversification [54,55]. Genomic surveillance continues to play a major role in unveiling the genomic signatures signaling potential adaptation of emerging lineages.

Vaccines against mpox

There are several orthopoxvirus vaccines available. 'First-generation' and 'second-generation' vaccines contain a live poxvirus ≠ vaccinia – that is closely related to the smallpox virus and can replicate in human cells, while 'third-generation' vaccines contain vaccinia viruses attenuated through serial passages in non-human cells or by laboratory deletions of selected genes [56,57].

For a long time, the first-generation Dryvax, a live vaccinia virus vaccine derived from the NYCBH strain (Wyeth Laboratories, Inc., Marietta, Pa), was the only FDA licensed vaccines. Dryvax, which was produced from the lymph or skin of inoculated animals, was used to vaccinate military personnel and selected civilian population groups [58].

Second-generation smallpox vaccines, also based on replication-competent viruses (i.e. ACAM1000 and ACAM2000 vaccinia virus-based vaccines), were produced by modern cell culture techniques, demonstrating an acceptable safety profile, but still with the potential for severe adverse events [33,58,59].

Finally, third-generation vaccines, based either on replicating (i.e. LC16m8) or replication-deficient vaccinia viruses (MVA, NYVAC), were developed. The use of LC16m8 in immunocompromised has been questioned [60], whereas MVA – modified vaccinia Ankara – appear to have a consolidated safety profile [33].

The hypothesis that smallpox vaccination may protect against mpox is consistent with the observation of an increase in the number of cases of mpox observed in children and young adults in affected African countries after the end of smallpox vaccination in the second half of the 1970s. In fact, since immunity against smallpox may last for up to 50 years since vaccination, the older generations still appear to be protected against mpox [57]. Consistently, recent studies have reported that serum antibodies elicited by first-generation smallpox vaccines can neutralize the current MPXV more than 40 years after vaccine administration [61].

However, prior to the current outbreak, only one study conducted in the DRC evaluated the protection induced by the now-obsolete first-generation vaccines, providing an estimate of vaccine effectiveness against mpox around 85% [62]. A retrospective study conducted in the Netherlands has now found a protective effect on those who had been vaccinated with first-generation smallpox vaccine, with a vaccine effectiveness of 58% (95% CI: 17–78%) against moderate/severe mpox [63].

Evidence of the protection conferred by third-generation vaccines is now increasingly available. First of all, MVA was known to protect non-human primates from mpox challenge [33]. Soon after the beginning of the multi-country outbreak in 2022, a study investigated the genetic variation with respect to orthologous immunogenic vaccinia-virus proteins, anticipating data on immune responses induced by VACV-based vaccines, including the currently available MVA-BN and ACAM2000 vaccines, showing a high cross-reactivity against the newly observed monkeypox viruses [64]. In the last year, other vaccine effectiveness studies have been published, mainly on the MVA vaccine (called Imvanex in the EU, Imvamune in Canada, and Jynneos in the US). Two studies from the US found VE between 75% and 85%, with protection being higher after a full vaccination cycle (2-doses) [65,66]. Moreover, a nationwide case–control study found lower VE, with the protection provided by full vaccination at 66% (95%CI 47–78%) and the protection from partial vaccination (1 dose) at 35% (95% 22–47%) [67]. In addition, another study compared the incidence of monkeypox among persons who were unvaccinated and those who had received ≥1 JYNNEOS vaccine dose, showing that the incidence among unvaccinated persons was 14 times that of those who received 1 dose of JYNNEOS vaccine ≥14 days earlier [68]. Finally, a study in the UK found vaccine effectiveness against symptomatic mpox at least 14 days after a single dose to be 78% (95% CI 54 to 89) [69].

Finally, little information from comparative studies is available. A recent review investigated the efficacy of the MVA vaccine and ACAM2000 vaccine, by analyzing their rates of humoral cell responses and adverse events, and found that ACAM2000 showed a lower

elevation of neutralizing antibodies than the JYNNEOS vaccine, and the latter was associated with lower adverse effects reactions [70].

Before the recent epidemic crisis, most countries had stockpiled more second-generation than third-generation smallpox vaccines [71]. However, adverse events associated with second-generation vaccines may prevent their use in children, pregnant women, immunocompromised, and persons with skin conditions such as eczema. Thus, the demand of third-generation vaccines rapidly increased, though the number of doses available was initially limited and not sufficient to satisfy global demand. For this reason, a mass vaccination campaign appeared not to be feasible. Furthermore, the epidemic was partially contained, remaining mainly concentrated within high-risk population groups, thus pre- and/or post-exposure vaccination of specific target groups is highly preferable to large-scale vaccination strategies.

Targeted (pre-exposure) vaccination of high-risk groups (i.e. GBMSM) with multiple partners might be implemented to contain outbreaks, and specific categories of health care workers, such as those working with viral cultures, could also be protected through vaccination.

A ring vaccination approach, where the vaccine is offered to those exposed through close contact with an mpox infected person possibly within 1–4 days after exposure [72], might also be considered. In theory, a ring vaccination strategy could be successful, since mpox spreads slower than airborne viruses and has a long incubation period [73]. However, even though ring vaccination may utilize resources more efficiently, the success of such approach relies on rigorous and efficient testing and contact tracing activity [71,74]. A recent study assessed contact tracing outcomes in the US before and after access to the mpox vaccine was expanded from post-exposure prophylaxis for persons with known exposure to include any persons at high risk for acquisition. The study found that during the period when mpox cases among MSM increased and vaccine access expanded, contact tracing became less efficient at identifying exposed contacts, as the proportion who named at least one contact decreased by 40% during the 2 time periods, highlighting the challenges of such an approach [75].

During the recent outbreak, ring vaccination of case's contacts has been adopted in several countries, and observational data suggest that, even though it may lower the risk, breakthrough infections may still occur [71,76].

Mathematical models suggest that ring vaccination can be successful if infectious cases are rapidly diagnosed and a high fraction of (primary and secondary) contacts is identified by contact tracing [77], especially if ring vaccination is combined with traditional measures such as isolation and self-quarantine [78]. Furthermore, it should also be considered that while second-generation vaccines are intended to be administered as a single dose, MVA is a 2-dose vaccine (given 28 days apart).

There are several points in favor of a targeted strategy using combined pre- and post-exposure vaccination, with special regard to the use of ring vaccination to contain mpox outbreaks. Smallpox global eradication initially used a strategy of mass vaccination campaigns to achieve 80% vaccine coverage in each country, then followed by case finding with ring vaccination of all known and possible contacts [56]. However, several factors may justify a ring vaccination strategy against mpox, such as the relatively low number of cases reported so far, the restriction of cases to certain communities, and the lower attack rate/R_0 compared with that of smallpox. In this regard, experience with other infectious diseases, such as Ebola, confirmed that ring vaccination may enhance standard public health measures of contact tracing, isolation, and community engagement, and is effective when such measures are in place [79,80].

In order to efficiently control human-to-human transmission, however, there is a need to guarantee vaccine equity and ensure global access to vaccines, and not only to countries that can afford to pay excessive prices, just because there is high demand. For COVID-19, 7 months after the first vaccines entered the market, ten countries still accounted for 77% of the globally administered doses, with a few countries purchasing far more vaccine than they could possibly use [81,82]. This has proven to be an ineffective global health response as pathogens do not respect borders [83]. Because smallpox/mpox vaccinology is an area that has benefited from a relatively high quantity of funds, which has led in the past decades to the development of second- and third-generation vaccines, and because the current outbreak is currently only affecting subgroups of the general population, vaccine manufacturers should be able to meet the vaccine demand across the globe.

Conclusion

On 23 July 2022, the current mpox outbreak was declared a Public Health Emergency of International concern – the WHO's highest global alert level [47]. This declaration was lifted on 11 May 2023, following a steady decline in the overall number of detected cases globally [84]. Until now, most cases reported in high-income countries have been identified among GBMSM; however, 'spillover' to the general population from currently affected population subgroups cannot be excluded. In addition, persistent virus circulation in wild animal reservoirs and human communities in Africa should be kept under attention. Of note, monitoring of animal populations in close contact with humans in newly-affected countries must also be considered, in light of the recent evidence of

human-to-animal transmission [85–87]. Though unlikely to be major drivers, differences in the surveillance systems and health care access may play a role in the different epidemiological characteristics of mpox cases observed between affected populations in Africa (higher proportions of infections in children and females) and outside Africa. Virus adaptation in humans, which may lead to changes in virus characteristics (i.e. transmissibility or virulence) during human-to-human transmission chains should be strictly monitored. Finally, vaccination of high-risk groups remains key, especially now that there is strong evidence of the cross-protection provided by smallpox vaccines against mpox.

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