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REVIEW ARTICLE

Monkeypox 2024 outbreak: Fifty essential questions and answers

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Abstract

As the world still vividly recalls the previous monkeypox (mpox) outbreak that impacted over 120 countries worldwide with more than 99,000 cases in 2022, we are now facing a second wave of infections from the monkeypox virus (MPXV), characterized by an exponential increase in cases. The current 2024 outbreak has already recorded more than 20,000 cases in Africa, marking a dramatic escalation compared to previous outbreaks. The predominance of the newly identified clade Ib variant, first detected in the Democratic Republic of the Congo (DRC) and now identified across multiple African nations and beyond, underscores its enhanced transmissibility and potential for international spread, evidenced by cases in Sweden and Thailand. The World Health Organization (WHO) declared on August 14, 2024, the current mpox outbreak a Public Health Emergency of International Concern (PHEIC), calling for heightened global public health measures. The ongoing pattern of unusual, frequent, and extensive outbreaks of mpox with potential global implications poses significant questions. This review addresses, in the format of 50 questions and answers, the 2024 mpox outbreak, detailing its characteristics, epidemiological data, and impact compared to previous outbreaks. It comprehensively explores critical questions related to MPXV virological characteristics, immunological response, clinical manifestations, epidemiology, diagnostics, and available treatments. The review also documents the significant and evolving challenges posed by the current mpox outbreak, highlighting its scale, spread, and public health response.

KEYWORDS
monkeypox, outbreak, poxvirus, upsurge, viral zoonosis, zoonotic infection

For affiliations refer to page 3303.

1 | INTRODUCTION

Monkeypox virus (MPXV) is a double-stranded DNA virus belonging to the *Orthopoxvirus* genus within the *Poxviridae* family, along with 11 other poxviruses, including the variola virus. MPXV infection induces monkeypox disease (mpox) that initially presents with flu-like symptoms often accompanied by cough and swollen lymph nodes. A skin rash typically develops within a few days of the fever waning. While the symptoms are generally mild and self-limiting, individuals with compromised immunity, children, and pregnant subjects are at increased risk for severe complications and mortality.[1–4]

Currently, we are facing a new mpox outbreak, characterized by the emergence of a novel variant, clade Ib, which has significantly challenged global public health frameworks. This outbreak, primarily fueled by the new variant that transmits rapidly through close contact, has recorded a total of 20,720 cases alongside 582 deaths across 13 African Union Members since early 2024, highlighting its severe impact and widespread nature.[5]

The World Health Organization (WHO) has reacted to this escalating threat by declaring a Public Health Emergency of International Concern (PHEIC) on August 14, 2024, due to the rapid cross-border spread of the virus in African countries.[6] This declaration underscores the gravity and potential for international spread, particularly after confirming cases in Sweden and Thailand, showcasing the virus's reach beyond endemic regions.[7,8]

Historical data from prior outbreaks have illustrated that clade I of MPXV generally presents higher morbidity and mortality rates than clade II. In that respect, the current 2024 outbreak in Africa associated to clade Ib has a case fatality rate (CFR) of approximately 3%, whereas the CFR of the 2022 global outbreak (associated to clade IIb) was 0.2%.[5]

The current 2024 mpox outbreak marks the second time the disease has spread on a relevant scale following the major 2022 outbreak. In 2022, WHO declared the mpox outbreak a PHEIC following a sudden surge of mpox cases that rapidly spread worldwide, with over 99,000 confirmed cases across 122 countries. The 2022 outbreak was characterized by its broad geographic spread. It represented a significant departure from previous outbreaks, which were contained mainly in endemic regions of Africa and primarily impacted children in small, rural communities. Although the first PHEIC was lifted in May 2023, the 2024 outbreak re-emerged, raising renewed concerns due to its rapid transmission and potential for widespread global impact.[9–11] WHO has linked the mpox outbreak to climate change, citing the shrinking space between human and wildlife habitats and increased ecological fragility. Rising global temperatures and environmental changes have contributed to the intensification of extreme weather events, which, in turn, have been associated with increased mpox cases. The destruction of ecosystems and socioeconomic disparities further heighten the risk of transmission, particularly among vulnerable populations.[12]

This review seeks to deliver the most up-to-date scientific insights on MPXV and the ongoing mpox 2024 outbreak. It addresses 50 critical questions about its virological characteristics, immunological response, clinical manifestations, epidemiology, diagnostics, and available treatments. Additionally, this review examines the potential causes and far-reaching consequences of the current mpox outbreaks.

2 | CHARACTERISTICS OF THE CURRENT 2024 MPOX OUTBREAK

2.1 | What are the characteristics of the current 2024 outbreak, and how does it differ from the previous one in 2022?

The current 2024 outbreak of mpox accumulates a total of 20,720 cases (3331 confirmed; 17,389 suspected), and 582 deaths reported from 13 African Union Members since the beginning of 2024. The Democratic Republic of the Congo (DRC) documented 19,667 cases, including 575 deaths. This represents the highest number of cases in the African continent. Mpox cases have also been reported in 2024 in Burundi (702 cases), Congo (162), Central Africa Republic (45), Nigeria (39), Cameroon (35), Côte d'Ivoire (28), South Africa (24), Liberia (6), Rwanda (4), Uganda (3), Kenya (2), and Gabon (1) (Figure 1).[5] In DRC, the current outbreak initially involved the endemic strain, clade I. However, a new variant, clade Ib, which appears to transmit more quickly through close contact (with prolonged skin-to-skin contact involving virion-rich lesion sites as the primary mode of transmission), is now fueling the spread of the disease. The new clade Ib, first detected in DRC and reported in April 2024, has also been confirmed in cases across Burundi, Rwanda, Uganda, and Kenya.[5] The infection counts have exponentially increased since the beginning of 2024, and the virus is quickly spreading (Figure 1). However, the actual size of the outbreak may be larger than what has been reported due to under-ascertainment and under-reporting. The increase in cases raised concerns regarding the potential for the international spread of clade Ib. In that respect, the first two cases of MPXV clade Ib were confirmed in Sweden and Thailand in August 2024.[7,8]

The current 2024 outbreak has notable differences compared to the previous 2022 outbreak. Firstly, in 2022, MPXV clade IIb was the main elicitor.[11,13,14] It is hypothesized that the new Ib strain may display increased contagiousness and a more severe clinical course.[5,14] In the current outbreak, the majority of cases and deaths occurred in vulnerable populations, particularly children under the age of 15, who accounted for a prominent part of all deaths, while the 2022 outbreak predominantly affected adults.[5,14] The ways of mpox transmission also differ between the 2024 and 2022 outbreaks, and these will be addressed in Section 4.

2.2 | What is the classification of the current 2024 mpox outbreak according to WHO?

On August 14, 2024, WHO declared a public health emergency of international concern (PHEIC) for the second time in 2 years, citing the increase in mpox cases in DRC and their rapid spread to neighboring

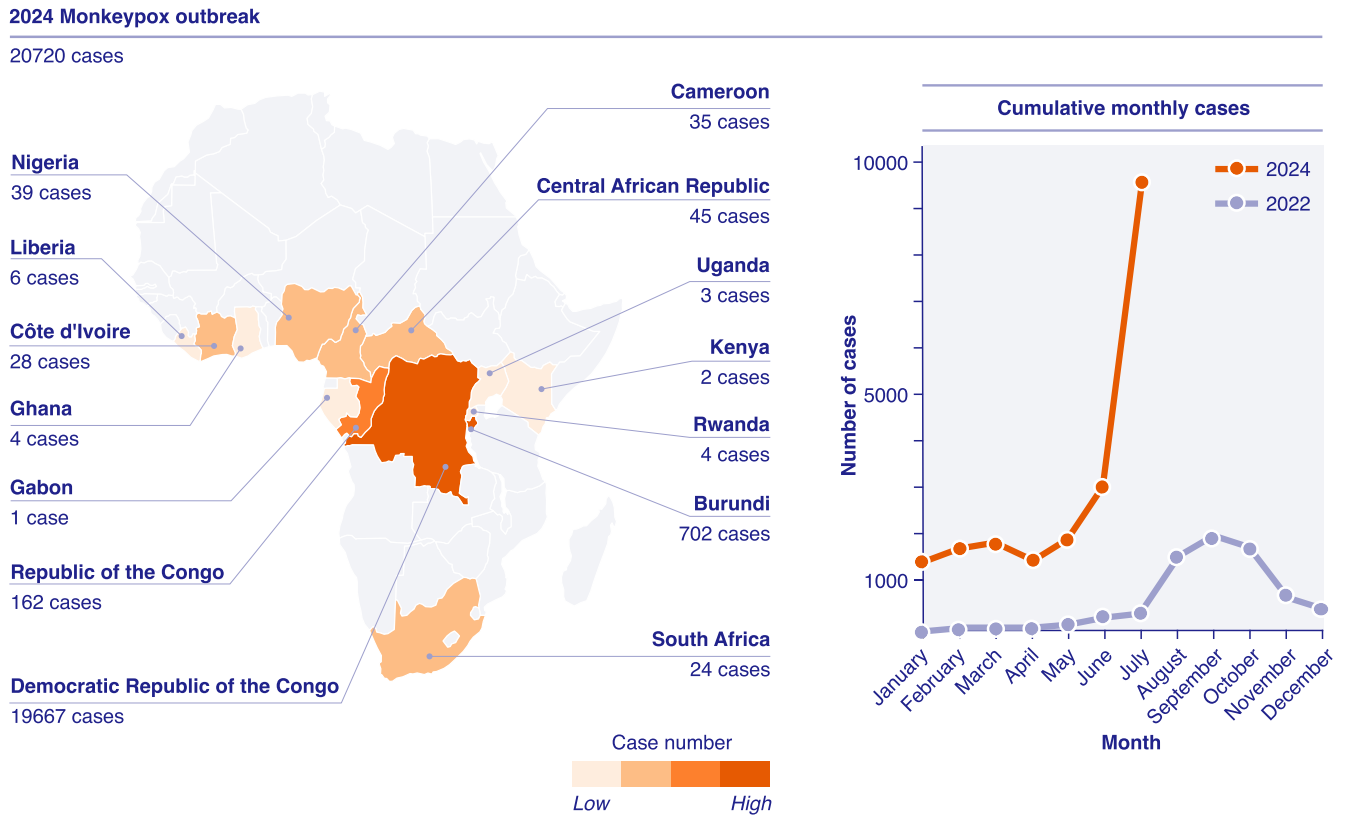

FIGURE 1 Map of Africa displaying the countries with reported mpox cases in 2024 (up to September 2024). The graph on the right illustrates a comparison of cumulative monthly mpox cases in Africa between 2024 and 2022.

countries. This classification represents the WHO's highest alert level and aims to accelerate international public health measures and cooperation.[6]

2.3 | What led to the decision to declare a public health emergency of international concern (PHEIC) for the second time?

While most mpox cases are concentrated in rural areas close to tropical rainforests in Central and West Africa, there have been reports of cases occurring in urban areas in Africa in recent years. In 2022, cases of mpox were documented in at least 120 countries worldwide. A minimum of 100 countries reported the occurrence of mpox for the first time. Subsequently, WHO designated the situation as a PHEIC in July 2022.[13,14] The PHEIC concluded in May 2023, coinciding with a notable decline in cases observed from April 2023 onwards. From September 2023 onwards, there was an increase in the number of case notifications from DRC and neighboring countries. By 2024, the caseload for the year's first 6 months had reached the same level as the total for the preceding year.[15] Moreover, as the spread of cases in Africa has been associated with a novel strain (Ib), these combined factors resulted in the decision to declare a PHEIC by WHO for the second time.[6,16]

2.4 | What is the case fatality rate (CFR) of mpox in the current 2024 outbreak compared to the previous one?

Historically, clade I has been reported to have higher morbidity and mortality rates than clade II.[17] The current 2024 outbreak in Africa has a CFR of approximately 3%, whereas the CFR of the 2022 global outbreak was 0.2%.[5] Although the current extent of under-detection and under-reporting of cases in affected countries is unknown, it is believed to be significant. As a result, the reported number of cases is likely an underestimate of the actual number of infections, while the CFR may be overestimated.[17] Despite these figures, significant uncertainties persist regarding the principal transmission routes, transmissibility, severity, and natural history of mpox. The clinical presentation of cases in DRC and neighboring countries remains underreported, and detailed surveillance data are lacking.[18] Therefore, it is premature to draw definitive conclusions about whether the higher CFR in Africa reflects a trend of increased severity or is an artifact of incomplete surveillance data. Continued monitoring and research are essential to provide more accurate assessments of mortality rates and disease characteristics as the outbreak progresses.

3 | PREVIOUS MPOX OUTBREAKS: FEATURES AND OUTCOMES

3.1 | What is known about the 2022 mpox outbreak? Which countries were most affected?

In May 2022, a mpox outbreak was initially notified. On July 23, 2022, WHO declared this mpox outbreak as PHEIC[4,19,20] for the first time to advise on the global risk to human health, requiring a coordinated international response.[21] Since then, the number of reported mpox cases has escalated. By October 7, 2022, the number of global cases increased to 71,096 worldwide, with more than 98% reported in locations with no historical cases of mpox.[9,10] Just over 1 year, more than 99,000 confirmed cases have been reported in 122 countries in all 6 WHO regions, and a total of 207 deaths (Figures 2 and 3).[11] The most affected countries globally are the United States of America (USA) (>33,000 cases), followed by Brazil (>11,000 cases) and Spain (>8000 cases) (Figure 2).[9–11] However, in May 2023, the first PHEIC of mpox was lifted due to the significant decrease in the overall number of reported cases and because no changes were detected in the severity of the disease or the associated clinical manifestations.[22,23]

3.2 | Was the 2022 mpox outbreak outside endemic areas the first of its kind in history?

Since the identification of mpox in Denmark in 1958 in monkeys,[9] and the first reported human infection in 1970 in DRC, the transmission of mpox was mainly based on animal-to-human interaction.[4,20,24] Between 1970 and 1971, six human cases of mpox were reported in Africa, although the disease remained exclusively localized, with limited small outbreaks in endemic African countries (Figure 4).[9] Since then, mpox has shown a gradual and sporadic occurrence in Africa: mpox clade I in central and east Africa and mpox clade II in west Africa, where the disease is endemic.[19] Nevertheless, mpox cases were occasionally exported to non-endemic countries, as in 2003, when an outbreak in the midwestern USA (Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin), probably related to imported African wild animals, which transmitted the disease to prairie dogs, and from them to humans (Figure 4).[19] In recent years, the number of cases per year has increased in endemic areas, with specific local outbreaks. Of relevance was the outbreak reported in Nigeria (2017–2018), and as a consequence, people from different countries traveling through Nigeria became infected, and the infection spread to their home countries. Between 2018 and 2021, mpox was only detected on eight occasions in four countries outside Africa, all due to travel to endemic regions. However, secondary and tertiary person-to-person infections were also reported, with no deaths outside Africa.[25–27] Therefore, the 2022 mpox outbreak outside endemic areas, although not the only one in history, has particular characteristics never seen before (Figure 4).

3.3 | What are the defining features of previous outbreaks (before 2022)?

Between 1960 and 1980, no outbreaks of mpox were detected in humans.[9] After 1980, the number of cases of mpox in central and

Country	Cases	Country	Cases
USA	33435	Switzerland	579
Brazil	11212	Ecuador	557
Spain	8084	Guatemala	405
France	4272	Austria	348
Colombia	4249	Taiwan	340
Mexico	4124	Australia	334
UK	3952	Israel	314
Peru	3875	Sweden	299
Germany	3857	Bolivia	265
DRC	3104	Ireland	249
China	1931	Japan	247
Canada	1557	Panama	239
Chile	1449	Costa Rica	225
Netherlands	1304	Poland	223
Portugal	1193	Vietnam	202
Argentina	1149	Denmark	198
Italy	1049	South Korea	161
Nigeria	898	Ghana	127
Belgium	810	Paraguay	126
Thailand	805	Norway	106

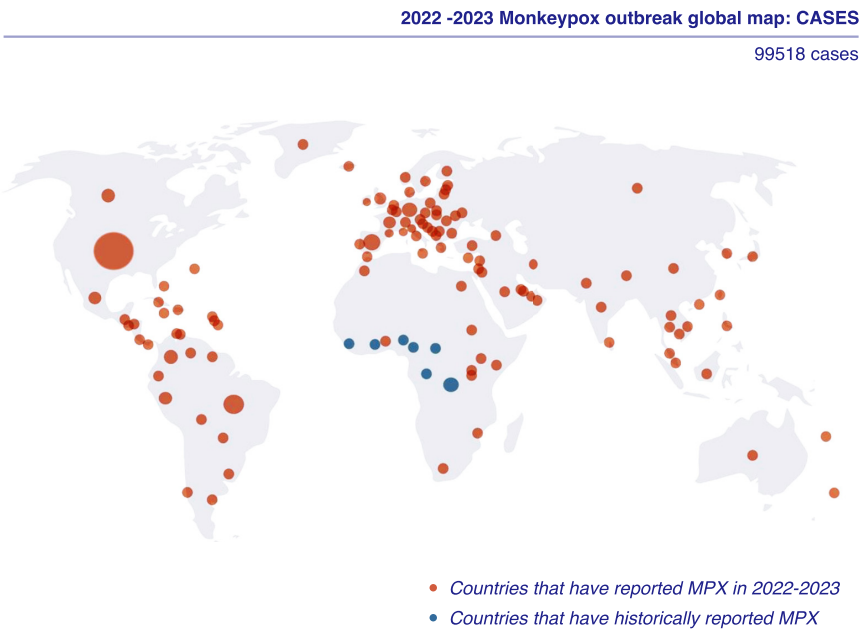

FIGURE 2 Worldwide distribution of confirmed mpox cases in the 2022 outbreak. The table presents data from 40 out of 122 countries with the highest number of confirmed mpox cases. Map created using Biorender with academic licensing.

Country	Deaths	Country	Deaths
USA	60	South Africa	3
Mexico	34	Argentina	2
Peru	20	Belgium	2
Brazil	16	Republic Of The Congo	2
DRC	10	Guatemala	1
Thailand	10	Austria	1
Nigeria	9	Japan	1
Vietnam	8	Panama	1
Cameroon	5	Czechia	1
Ghana	4	Central African Republic	1
Spain	3	India	1
Chile	3	Sudan	1
Portugal	3	Cuba	1
Ecuador	3	Mozambique	1

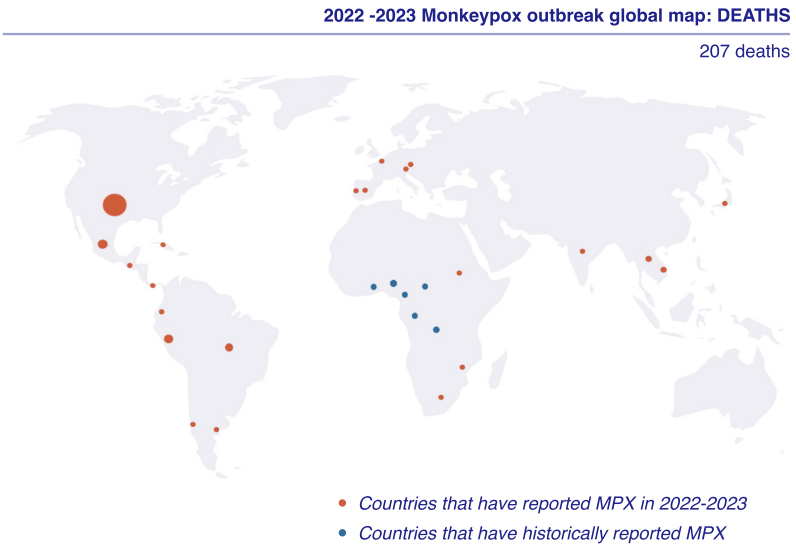

FIGURE 3 Global distribution of confirmed mpox fatalities in the 2022 outbreak. Map created using Biorender with academic licensing.

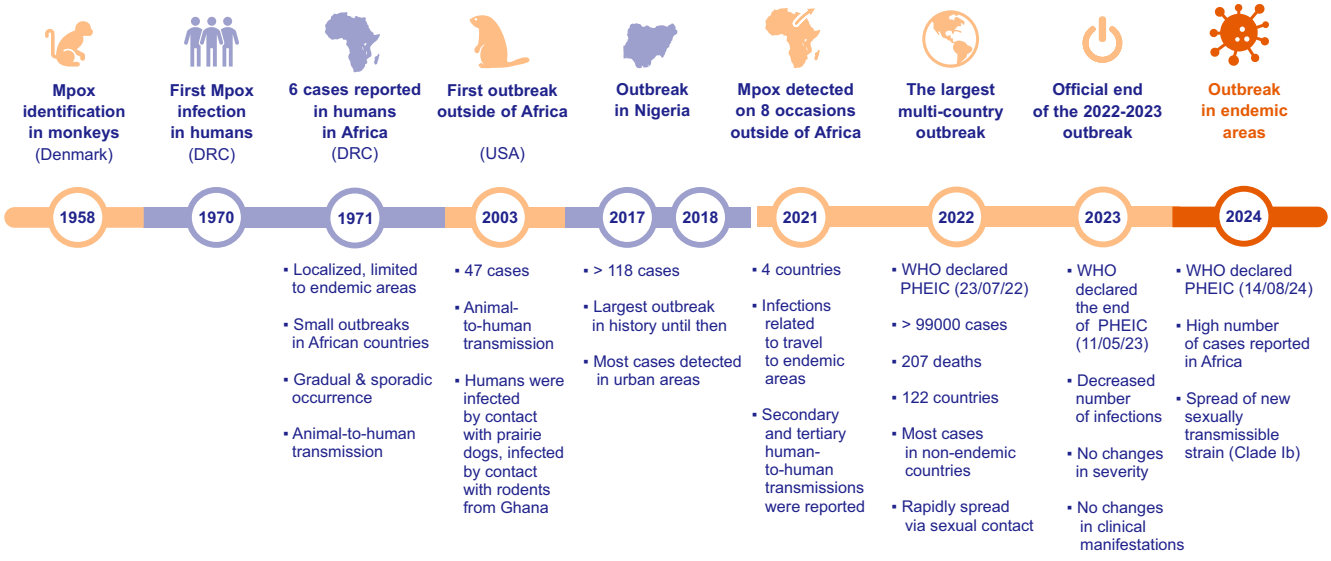

FIGURE 4 Mpox historical overview: Timeline outlining key dates in mpox history, from the discovery of MPXV in 1958 to the ongoing 2024 outbreak.

west African countries increased, mainly associated with animal-to-human infections, probably due to closer interaction between them in rural areas related to multiple causes such as deforestation, urbanization, migration, animal trade, habitat destruction, and the end of smallpox vaccination.[26,28] Moreover, as for the 2003 outbreak in the USA, limited and isolated outbreaks outside endemic countries were reported.[29] In 2014, the number of cases in endemic areas increased significantly, surpassing previous data in those regions over the last 40 years.[26] During 2017–2018, an outbreak of 118 cases was reported in Nigeria, and since then, only sporadic outbreaks of mpox cases have been reported outside endemic areas.[27] Thus, before 2017, mpox outbreaks occurred mainly in endemic countries in central and west Africa, with the sustained transmission in local animal reservoirs and sporadic transmission in human populations.[20] However, after 2017, there was a shift in the transmission pattern. Indeed, in Nigeria, where the largest outbreak in history until that year was reported, most cases were detected in urban areas, suggesting new risk factors (Figure 4).[27,30] Between 2018 and 2021, most outbreaks occurred mainly in six African countries: Cameroon, Central African Republic, DRC, Nigeria, Congo, and Sierra Leone,[9] with more than 3000 suspected cases/year, with a peak in 2020 with more than 6000 suspected cases and more than 200 deaths.[26] Therefore, most of the outbreaks before 2022 were localized in endemic countries in Africa, being sporadic, restricted to a specific location, and affecting mainly children under 15 years of age,[28] primarily occurring in small and remote villages in rural areas, with very limited outbreaks outside these areas.[9]

3.4 | How did the 2022 outbreak differ from those that occurred before it?

A defining characteristic of the 2022 mpox outbreak was that it appeared suddenly and spread rapidly worldwide.[28] Since May 6, 2022, when the first case of mpox outside Africa was reported, numerous cases have emerged in different countries in people with no history of traveling to endemic countries or contact with infected animals (Figure 4).[9,21] Another essential feature of the 2022 mpox outbreak was that most cases were reported in non-endemic countries and very diverse geographic areas, in contrast to most previous mpox outbreaks, which were mainly located in small endemic areas in Africa.[11,28] In addition, during the 2022 outbreak, unprecedented global transmissions occurred through human-to-human interaction,[31] primarily through sexual contact, affecting—but not exclusively—men who have sex with men (MSM),[28] who contributed to the rapid transmission of the disease.[4,11] The 2022 mpox outbreak has been the largest in magnitude and geographic areas.[20] Most cases in the 2022 outbreak were caused by mpox from clade IIb.[20] In contrast, the previous outbreaks in Africa originated from both clade II and clade I, with clade I being more virulent than clade II and more associated with heterosexual transmission linked to commercial sex work.[19] The predominance of clade IIb infections during the 2022 outbreak could explain the different clinical presentations compared to previously documented outbreaks, being less severe, with lesions more frequently located on genitals and mucous membranes, as well as proctitis, compared to clade I infections, with more complications such as sepsis, pneumonia, or encephalitis.[9,19,20]

4 | MPXV: CHARACTERISTICS OF THE VIRUS AND WAYS OF TRANSMISSION

4.1 | How is MPXV classified, what are its phylogenetic traits, and what sets the MPXV in the 2024 outbreak apart from previous strains?

MPXV is renamed by the International Committee on Taxonomy of Viruses (ICTV) as *Orthopoxvirus monkeypox* and is classified in *Orthopoxvirus* genus, *Chordopoxvirinae* subfamily, *Poxviridae* family along with 11 other poxviruses, including the variola virus, the etiological agent of smallpox.[32] While MPXV was previously classified into three clades—clade I, IIa, and IIb,[33] in the new taxonomy, MPXV has phylogenetically distinct two clades: clade I (previously designated as clade 1/Central African/Congo Basin) and clade II (previously designated as clade 2/West African). Clade I MPXV causes higher CFR than clade II MPXV.[34] Following shotgun analysis of orangutan specimens from Sumatra collected in 1965 at a zoological research museum in Germany, MPXV clade IIa was detected in the samples, and these sequences were determined to be closely related to the genome derived from the 1965 Rotterdam Zoo outbreak. The study demonstrates that sequence analysis of historical samples can provide significant insights into the epidemiology of mpox.[35] The meta-analysis indicates that MPXV behaves as an opportunistic pathogen in immunocompromised individuals. However, no direct study has identified which genes in the genome are involved.[36] In another meta-analysis, MPXV clade IIb exhibited higher infectivity but was associated with mild disease symptoms and a low mortality rate.[37]

Before the MPXV global outbreak in 2022, clade I MPXV infections were predominant, with most cases reported in Central Africa. As outlined, clade II has two subclades designated as IIa and IIb. Clade IIa was detected in the 2003 mpox outbreak in the United States, while clade IIb caused the 2017–2019 mpox outbreak in Nigeria and the 2022 global mpox outbreak.[38] The clade IIb has four lineages: A.1, A.1.1, A.2, and B.1, which includes the MPXV genomes from the global 2022 outbreak.[33,39] There are 46 single nucleotide polymorphisms (SNPs) determined in clade IIb lineage B.1, which represent strong mutational bias: 26 of them (14 nonsynonymous, 10 synonymous, and two intergenic) were identified as GA > AA, and 15 (nine nonsynonymous and 16 synonymous) as TC > TT nucleotide replacements. Among the 46 SNPs identified as specific to the clade IIb lineage B.1, 24 nonsynonymous mutations distinguish the clade from the closest reference sequence. Of these mutations, the amino acid changes D209N, P722S, and M1741I in the immunogenic surface glycoprotein B21R of MPXV, which contains immunodominant epitopes and serves as a target for antibodies, are thought to alter host interaction, thereby facilitating transmission.[33,40,41]

MPXV encodes approximately 190 genes and 187 ORFs, which can be divided into three genomic parts: central region, which encodes virus replication/transcription genes; left terminus, and right terminus, which encodes immunomodulatory/host range protein genes.[41,42] The left and right termini of the MPXV genome are variable regions and play a role in host range determination and pathogenicity of orthopoxviruses.[41] A study showed that lineage B1-specific mutations are present in the right (13 mutations) and left (8 mutations) variable regions.[41] APOBEC3-like mutations are also identified in MPXVs, accounting for 16 out of 18 synonymous mutations and 23 out of 24 nonsynonymous mutations.[33,41] D2L-like, OPG023, OPG047, OPG071, OPG105, OPG109, A27L-like, OPG153, OPG188, and OPG210 proteins of MPXV are found to be more prone to mutation.[41] A recent study showed that there are MPXV 25 genes subjected to positive selection (J2L, D2L, D9L, D13L, O2L, C2L, C7L, C15L, F3L, Cop-E5R, G8L, G9R, G10R, M5R, L3R, H2R, A12R, A31L, A47R, A51R, B2R, B6R, B16R, B21R, and J2R) and 60% of these mutations were located in left and right variable regions while the remaining were exhibited in the central region. Also, interspecies and intraspecies recombination events were detected in the MPXV genome, and 73.3% of recombination is present in variable regions of the viral genome.[43] In most comparisons, the dN/dS ratio was less than 1, indicating that most MPXV genes are under purifying selection. However, for 12 genes, the dN/dS ratio was greater than 1 in some comparisons between clades, suggesting that these genes are under positive selection. Four of these genes (OPG002, OPG023, OPG027, and OPG031) are associated with resistance to the host's immune system. Notably, the OPG027 gene

shows positive selection between clade I and clade II (IIa, IIb-A, IIb-B) but shows purifying selection among strains within clade II. This suggests that the gene underwent positive selection during clade I and II divergence but was under purifying selection during differentiation within clade II.[44] A study showed that clade IIb MPXV from the 2022 outbreak has non-randomly distributed 21 low-complexity regions (LCRs) consisting of 13 short tandem repeats (STRs) and 8 homopolymers, which are in lower frequency in the central region of the viral genome.[45]

As discussed in previous sections, the 2024 mpox outbreak is caused by a new MPXV lineage designated as clade Ib.[6,46] Unlike the 2022 mpox outbreak, which was caused by clade II MPXVs, the circulating virus in the 2024 mpox outbreak was identified as clade I. According to epidemiological studies, this recent outbreak has emerged in Central Africa, particularly DRC, possibly originated from zoonotic spillovers in forest regions and animal exposures, followed by subsequent human-to-human transmission from infected individuals.[47–49] Approximately 1 kbp (1114 nt) deletion in the MPXV genome that has been detected in the samples from the Kamituga outbreak in DRC culminated with complete deletion of the OPG032 (C3L) gene, and this gene deletion affects the accuracy of clade I-specific diagnostic PCR tests which is suggested by the Centers for Disease Control and Prevention (CDC). Considering that the novel genomes associated with the current mpox outbreak also carry this deletion, it is possible that all viral genomes identified as clade Ib thus far contain this deletion and, therefore, cannot be detected by the clade I-specific diagnostic tests.[46]

As of the 2024 mpox outbreak, clade I now includes two lineages: Ia and Ib; the latter is responsible for the current outbreak. Whole-genome sequencing data of MPXVs from a cohort study from DRC revealed that approximately 201.5 SNPs, 28 insertions, 81 deletions, 2 indels, 312.5 total variants, 158.3 amino acid changes, 81.66 intergenic variants, 72.16 synonymous mutations, 106 missense variants, 41.16 frameshift variants, and 3.33 in-frame deletions had occurred in clade I MPXV genomes in the 2024 outbreak. The result of the analysis of MPXV sequences detected in the latest mpox outbreak in DRC (Kamituga outbreak), hot spot mutations were identified in the proteins C9L (OPG047), I4L (OPG080), L6R (OPG105), A17L (OPG143), A25R (OPG151), A28L (OPG153), and B21R (OPG210). It has been reported that these mutations include consensus in-frame deletions, frameshift variants, synonymous variants, and amino acid substitutions.[47] The maximum pairwise patristic distance for the entire clade I was calculated as 4.89×10^{-4} substitutions per site; however, with the inclusion of genomes from the latest mpox outbreak in DRC, this rate increased to 7.55×10^{-4} substitutions per site. Furthermore, it is unveiled that APOBEC3-mediated cytosine deamination also occurred in the 2024 mpox outbreak.[48] Sequencing samples from the current MPXV outbreak is essential but complex because the viral DNA concentration is often below 0.5% of total reads, requiring millions of reads for accurate analysis. Although amplicon-based sequencing is commonly used, it can overlook large insertions and deletions, especially near the left and right inverted terminal repeats. Genomes with stretches of unknown nucleotides (Ns) in these regions should be re-evaluated using high-quality shotgun sequencing or capture-based methods. Perhaps, for this reason, specific epidemiological data may have been overlooked. However, we suggest that advancing techniques could help explain the higher transmission and mortality rates.[50]

4.2 | When was MPXV initially identified in history, and which species serve as its primary reservoir?

In 1958, in the Statens Serum Institut of Denmark, where the monkeys are used for polio vaccine production and research, a pox-like disease occurred among cynomolgus monkeys which had been received from Singapore. Following the outbreak, the epidemiological and clinical manifestations of the disease were described, and the virus was isolated and identified, leading to its designation as monkeypox.[51] The first MPXV isolation from wildlife, from squirrels, was reported in DRC in 1985.[52] The reservoirs of MPXV include a variety of mammals such as domestic pigs, African hedgehogs, gray short-tailed opossums, Southern/common opossums, squirrels, prairie dogs, woodchucks, dormice, African brush-tailed porcupines, Gambian giant rats, jerboas, and so on. Additionally, nonhuman primates like chimpanzees, rhesus macaques, orangutans, cynomolgus monkeys, mona monkeys, grivets, mangabeys, and Western red colobus monkeys also serve as reservoirs of MPXV. Animal-to-human transmission of MPXV has only occurred from orangutans, cynomolgus monkeys, string squirrels, and prairie dogs.[33,53–56] Cynomolgus monkey, ground squirrel, prairie dog, deer mouse, rope squirrel, Gambian pouched rat, African dormice, rats, mice, and Asian cynomolgus monkeys are used as experimental animal models.[55] Two recent papers revealed that the virus circulated earlier than previously known. Interestingly, orangutan specimens from a zoological research museum in Germany, dated 1965, as well as African rope squirrel samples from the Royal Museum for Central Africa in Belgium, collected in 1899, and from the American Museum of Natural History in the USA, tested positive for the MPXV genome.[35,57]

4.3 | When was mpox first documented in humans, and in which parts of the world is it considered endemic?

The first documented and confirmed human case of mpox occurred in DRC in 1970. The patient, a boy who presented with fever and rashes, was the first person in history to be diagnosed with mpox.[58] After the first human case of mpox, additional cases were reported in Liberia, Nigeria, and Sierra Leone between 1970 and 1971. Mpox is endemic in African countries, including DRC, Nigeria, Cameroon, the Central African Republic, Gabon, Ghana (identified in animals only), Côte d'Ivoire, Liberia, the Republic of the Congo, Benin, Sierra Leone, and South Sudan, according to

the WHO.[59] MPXV clades also differ among geographic regions of Africa: clade I is endemic to Central Africa, whereas clade II is endemic to West Africa.[60]

4.4 | How is MPXV transmitted, and what is the rate of its spread?

Numerous studies following our first review[33] have confirmed that direct transmission may occur through an extensive array of entry pathways: oropharyngeal mucosa, semen, urine, stool, saliva, and skin, with the latter being the predominant way of transmission (Figure 5).[61,62] Importantly, the virus was demonstrated in seminal and vaginal fluid even in the absence of skin lesions, but associated with serum or plasma presence, suggesting a role for passive diffusion.[62,63] Although women in general and cisgender women, in particular, make up a minority of mpox cases, vaginal and vulvar lesions related to sexual intercourse were observed.[64,65] In addition, mpox DNA was detected in all vaginal swabs, pointing to a potential new route of transmission from mother to child during delivery, as well as between heterosexual intercourse (Figure 5). Among homeless populations, who are generally more vulnerable to mpox development, transmission via shared utensils, clothing, and syringes has been suggested.[66] Furthermore, among these generally unvaccinated populations, a lower acceptance of vaccination was observed among MSM than among transgender females (74% vs. 78%) but higher than among cisgender men (52%).[67,68] These data show that both the socioeconomic dimension and awareness of the risk associated with exposure play a role in the prevalence of the transmission mode.[69] Wastewater is increasingly used to monitor the epidemiological evolution of diseases.[70] However, wastewater is also a significant transmission mode, particularly among wastewater treatment professionals, requiring further research on occupational risks (Figure 5).[71] Although no studies have been carried out on the viability of mpox in wastewater, the viability of other viruses from the *Poxviridae* family is established.[71,72]

The evolutionary dynamics of the transmission ratio now appear more precise, with an initial dominant spread within the MSM population, followed by a gradual and widespread transition to the heterosexual population as the number of cases increases.[73,74] Transmission from a nonhuman organism was also addressed, such as prairie dogs, Gambian pouched rats, dormice, rope, and tree squirrels (Figure 5).[33] Nonhuman primates, previously seen as a potential reservoir, are now considered accidental hosts.[75] A potential role for arthropods as vectors has been suggested, although no cases related to this transmission mode have been recorded to date.[76] R0, which is defined by the average number of infectious disease cases arising from transmission from a single infected individual, is difficult to determine because of its high variability and limited data, with a range during the 2022 epidemic from 1.54 in Belgium to 3.62 in Germany, and a median of 2.44 in non-endemic countries.[77] Data on new virus strain clade Ib, which is presumably more transmissible, are still lacking.

4.5 | Is mpox classified as a sexually transmitted infection (STI)?

Sexual transmission, mainly through close skin contact, is the main route of spread of the virus, with the highest prevalence observed

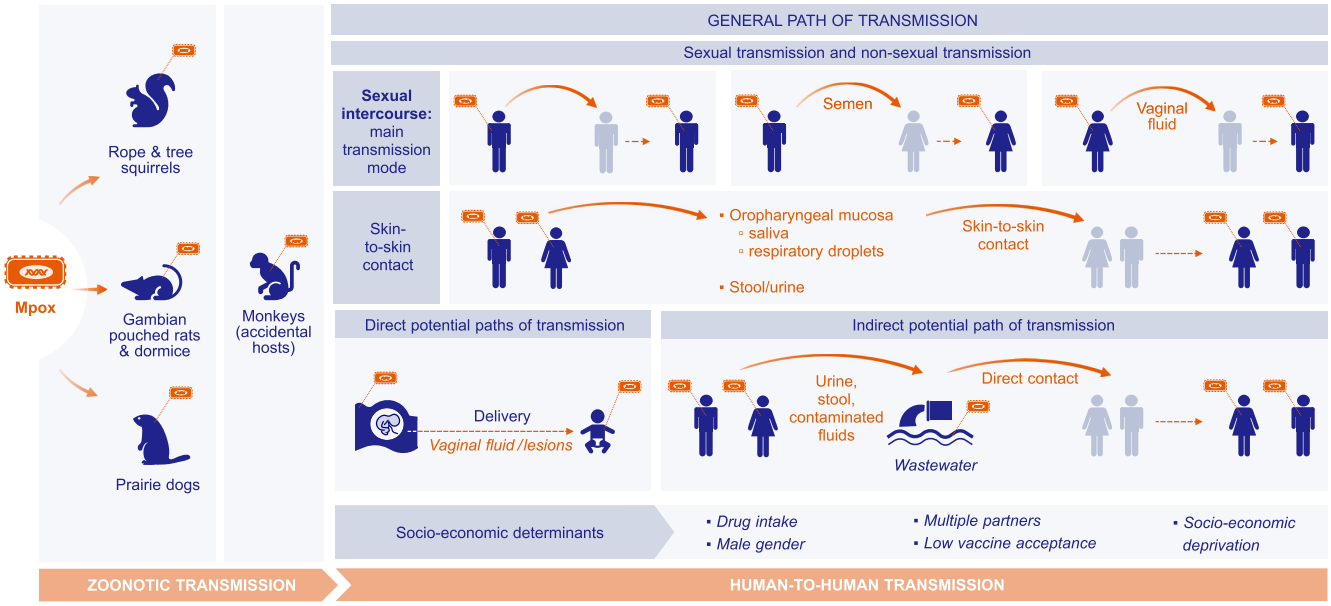

FIGURE 5 General insight of mpox transmission. The main path of transmission to the general population is mostly from skin-to-skin contact mainly during sexual intercourse among the MSM population. Zoonotic transmission is clearer as monkeys appear to be accidental hosts. Potential direct mother-newborn transmission during deliverance and indirect through wastewater have been suggested. Socioeconomic determinants directly influence the dynamic of Mpox transmission.

among MSM.[63] Risk behaviors may be more frequently encountered among MSM, notably the multiplicity of partners potentially fostered by participation in events such as pride events and sex parties.[61] As a rule, mpox prevalence is higher in patients who are also positive for other STIs, mainly HIV or have a history of previous STIs such as syphilis and hepatitis, supporting a pattern of risk-taking behavior.[63,64,78–80] Knowledge of viral clearance has been refined since 2022,[33] with a median duration of 25 days for clearance in skin lesions, 16 days in the oropharynx and rectum, 13 days for semen, and 1 day for blood after the onset of the first symptoms.[81] Additionally, replicating-competent viruses could only be isolated on samples with a viral load greater than 6.5 log10. Only skin samples showed a median viral load above this value, reinforcing the idea that the main route of transmission is via skin contact, especially during sexual intercourse, and, to a lesser extent, via contact with secretions.[81] Although sexual intercourse is often the central element in the anamnesis, it is essential to note that it acts above all as a factor favoring skin contact, as illustrated by the case of a mother breastfeeding her child.[82]

Based on the predominant transmission through skin contact, be it during sexual intercourse, some authors do not adhere to labeling mpox as a STI, an ongoing debate on this topic.[80,83,84]

4.6 | Is MPXV transmissible through the respiratory system, and can its DNA be found in saliva or oropharyngeal lesions?

Although transmission by respiratory droplets is possible, it remains quite infrequent, similar to other types of secretion, as the viral load is lower than in skin, and droplets can only travel a short distance.[54,81] However, this transmission mode should not be overlooked, particularly in occupational exposure, for example, healthcare professionals.[85–88] To date, several studies have improved our knowledge of the infectious risk of air contaminated by respiratory droplets.[86,87] For example, an association was demonstrated between the severity of symptoms and the salivary viral load, particularly concerning the evacuation of viral particles from the oropharyngeal area.[81,86,89] In one study, mpox DNA from exhaled air trapped on facemasks worn by patients was detected in 71% of cases, including two cases of viable, active virus, in the respiratory droplets collected.[86] Thus, facemasks, which concentrate viral particles from respiratory droplets, represent a genuine risk of transmission. Similarly, although viral DNA could be detected in the air while the patients wore FFP2 masks, the virus is usually non-viable.[86,90] The authors suggested that the viral load from respiratory droplets would be expected to remain below the contaminating threshold if facemasks are used, but not in the absence of a facemask, especially as the virus can remain viable for up to 90 h in the environment.[86] Moreover, the viral load in respiratory droplets fluctuates, as other compartments, depending on the severity of symptoms in the first days, rendering its proper assessment rather arduous.[89]

5 | MECHANISMS OF IMMUNE RESPONSE IN MPXV INFECTION

5.1 | General considerations about the immune response to MPXV

There were very few studies about the immune response to MPXV in infected individuals until recently. Some more information on humoral or cellular immune response against MPXV or its vaccine has been reported in the last 2 years. After developing an early innate immune response, both humoral and cellular immunity, including antibodies and memory B cells, as well as CD4+ and CD8+ T-cell responses, play a canonical role in recovery and long-term protection from smallpox and mpox.[91–94] In addition, antigen-presenting cells, such as dendritic cells and macrophages, innate lymphoid cells, and NK cells, play a role. As in almost all viruses, multiple immune evasion/escape mechanisms used by the MPVV play a role, as discussed below.

5.2 | What are the innate and adaptive immune responses to MPVX?

5.2.1 | Innate Immune Responses to MPXV[95–101]

The first line of defense, innate immunity, develops at the beginning of an active viral infection in the body. Interestingly, the very early innate immune response provides a viral entry route. Monocytes have been identified as the major route of poxvirus entry, and they may even play a role in the lethality generated by MPXV.[102] Monocytes are recruited to the sites of infection following their marked expansion and then play a role in viral spread. In mouse models, inflammatory monocytes have been predicted to be a possible vehicle for viral distribution. Similarly, human cell-based experiments showed that primary M2-like macrophages play a role in replication and distribution associated with virus spread. However, deletion of monocytes does not eliminate viruses from the host cell, indicating that specific other immune cells might also be involved in viral dissemination. The early role of neutrophils in the infection requires further studies, but the analyses of pustules reveal the involvement of neutrophils. Histopathologic findings in vesiculopustular lesions of mpox demonstrate necrosis, especially of the upper portions of the epithelium, and ballooning and reticular degeneration of keratinocytes, multinucleation of keratinocytes, nuclear enlargement showing, and a dense mixed inflammatory cell infiltrate with prominent neutrophil exocytosis.[103] CD94, a molecule preferentially expressed by NK cells, is essential for the resistance of C57BL/6 mice to mousepox.[104] Rhesus macaques infected with MPXV 2.5×10^6 PFU Zaire 79 strain showed increased NK cell frequency and absolute numbers in the peripheral blood and lymphoid tissues.

Another study showed that a moribund cynomolgus monkey exhibited neutropenia, excessive inflammatory responses, and high load viremia after experimental infection with the Liberia strain of

MPXV and concomitant bacterial sepsis.[105] Serum samples from mild ($n=4$), moderate ($n=5$), severe ($n=5$), and serious ($n=5$) patients with confirmed mpox were evaluated for cytokine profiling. All human cases had elevations in serum concentrations of IL1β, IL-1RA, IL-2R, IL-4, IL-5, IL-6, IL-8, IL-13, IL-15, IL-17, CCL-2, CCL-3, CCL-4, and CCL-5. However, only increased IL-2R, IL-10 concentration, and granulocyte macrophage-colony stimulating factor were significantly higher in serious cases compared to patients in other severity groups.[106] It was speculated that diazepam and alprazolam may augment the severity of poxvirus infections such as cowpox or mpox.[107]

In another study analyzing the transcriptomic response, HeLa cells were infected with three orthopoxviruses (MPXV, vaccinia virus, and cowpox virus) following 6 h. Differences in the cellular response were analyzed using microarray analysis. It was found that a majority of 96% of the assayed cellular transcripts remained unchanged. In total, 321 out of 30,484 individual genes and transcripts in MPXV-infected cells showed expression changes larger than 2-fold. While 219 out of 321 transcripts (68.2%) were up-regulated, 102 out of 321 transcripts were down-regulated. Infection-induced changes in the gene expression profiles of cowpox virus, MPXV, and vaccinia virus-infected cells were observed to be largely different. It was found that the most significant changes are histone mRNAs, leukocyte migration, and Toll-like receptor signaling transcripts. Findings might reflect an inadequate subversion of the hosts' antiviral response for orthopoxviruses.[108]

5.2.2 | B-Cell and Antibody Responses and Protection from MPXV

Following the innate immune response, adaptive responses or a second line of defense to control viral spread in the host body occur. The importance of B-cell-mediated immune responses in developing specific antibody responses is of prime importance because successful vaccinations against many viruses, including historical cases like smallpox, are based upon B-cell-mediated immunity. Within the same context, treatment with immunoglobulin preparations of vaccinated individuals was proposed to save patients from mpox infection.[109] This hypothesis was checked in monkey models and showed that smallpox-specific B-cell responses could protect against a lethal mpox infection in macaques.[91] Studies conducted on this cause revealed increased production of memory B cells and neutralizing antibody loads. A significant number of mpox proteins are recognized by immunoglobulins produced by B-cell responses from human vaccination protocols.[110] These proteins have functional characteristics and involvement in the infection and immune-regulatory responses associated with mpox and may be used for serological diagnostics. As in other viruses, IgM plays a vital role in the primary immune response, followed by IgG- and IgA-mediated secondary and long-lasting immune response against mpox.[111] A study including 37 confirmed mpox patients has investigated IgG and IgM responses regarding clinical signs and previous smallpox vaccination status of the patients.[93] IgG and IgM development profiles of smallpox-vaccinated and smallpox-unvaccinated patients with mpox are reported to be similar. IgG response appeared on Day 1 after the onset of rash in vaccinated patients, while IgG response was detected on Day 2 in unvaccinated patients. However, in both vaccinated and unvaccinated patients, IgM response was detected on Day 2 after rash onset, with a more rapid onset of IgM in unvaccinated patients. IgM titers were detectable until Day 77 and Day 126 in vaccinated and unvaccinated mpox patients, respectively. However, detectable IgG was observed until Day 147 in vaccinated and Day 139 in unvaccinated mpox patients from a total of 168 days analyzed.[93] These studies specifically highlight the need to extensively study specific antibody profiles in patients with mpox.

5.2.3 | T-Cell Responses to MPXV

CD4+ T cells play a vital role in cell-mediated immunity and mediating functional memory B-cell responses in mpox.[112,113] These cells are related to the production of IFN-γ and TNF following vaccination with vaccinia virus (VACV). T cells provide direct antiviral responses through CTLs, which have been found to kill infected macrophages directly and prevent further viral spread.[114] Similarly, CD8+ T cells eradicate virus-infected monocytes to control the viral load. An early expansion of activated effector CD4+ and CD8+ T cells that persist over time, regardless of HIV infection, developed a poxvirus-specific Th1 cell response. The expression of cytokines such as IL-1β, IL-1RA, IL-2R, IL-4, IL-5, IL-6, IL-8, IL-13, IL-15, and IL-17 increases following mpox infection in humans. A profile indicates mixed helper T-cell and regulatory T-cell responses in an inflammatory environment. A study of patients with HIV has shown that a compromised CD4+ cell count leads to higher risks of developing a severe mpox infection. The results were more explanatory when studies on patients with HIV with higher CD4+ cell counts were observed to lack severe mpox infection development.[115] Nevertheless, more insights into the observations are needed. In summary, T-cell responses in controlling *Orthopox* viral infections are significant and could be considered for vaccine design. Further studies are necessary to identify the relationship between CD4+ and CD8+ T-cell responses and specific B-cell responses with the severity of mpox infection in humans.

5.3 | What evasion mechanisms does MPXV use?

Immune evasion by MPXV is taking place similar to many other virus infections. It is based on mechanisms that disrupt host antiviral responses by using diverse strategies. These mechanisms can be listed as preventing the production of type I-II-III IFNs, blocking IFN-induced intracellular signaling, inhibiting the activation of NF-κB, inhibiting general immune cell activation, induction of apoptosis in immune cells, and blocking of the inflammasomes, namely the early IL-1beta and IL-18 production (Figure 6). MPXV can interestingly abrogate T-cell responses against other viruses and anti-CD3 stimulation.[116] Variola virus B17 and MPXV- B16 proteins inhibit type I

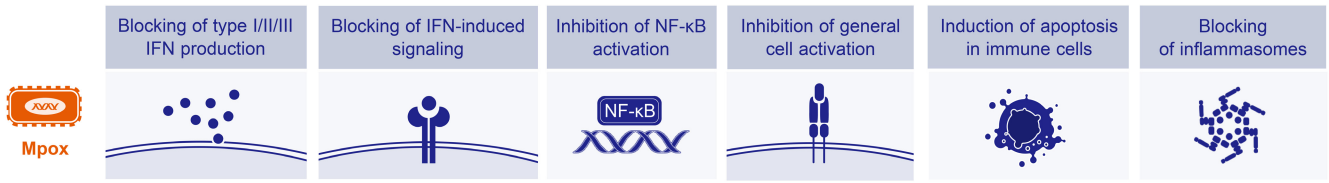

FIGURE 6 Mechanisms triggered by MPXV to disrupt host antiviral responses.

IFN-induced signaling.[117] Another study showed that the F3L gene of MPXV suppresses the immune type I interferon system by preventing the phosphorylation of PKR and eIF2alpha.[95] As another immune evasion mechanism, MPXV infection causes a loss in NK cell functions, including cytotoxicity capacity and secretion of IFN-γ and TNF-α, which may explain the death of MPXV-infected nonhuman primates.[118]

Poxvirus-encoded virokines act intracellularly or extracellularly, interfering with the response to infection within the cell, including the induction of an antiviral state, oxidative burst and apoptotic pathways, and the immune system through downregulation of immune recognition molecules, such as major histocompatibility complex (MHC) class I and CD4 as immune evasion.[119] For instance, IL-10 like virokine produced by multiple poxviruses presents a high identity with mammalian IL-10, showing important anti-inflammatory and immunosuppressive activities. Studies have demonstrated that deleting the gene that encodes IL-10-like virokine strongly reduces the infection effectivity of the virus.[120–122] Multiple poxviruses also produce IL-18 binding proteins (IL-18BPs) that can bind to mammalian IL-18, inducing the suppression of IFN-γ and cytolytic effector cells.[123,124]

BOX 1 Clinical signs and symptoms of mpox

- Incubation period: 5–21 days (mean: 9 days).
- Initial symptoms: fever, chills, headache, muscle pains, fatigue, sore throat, cough, and lymph node inflammation.
- Subsequent symptoms: skin rash.
- Other potential symptoms: oropharyngeal lesions, conjunctivitis, and blepharitis
- Symptoms last 2–4 weeks, and they usually are self-limited.
- Possible complications: neurological manifestations, ocular involvement, bronchopneumonia, digestive involvement, cardiovascular complications, urinary tract inflammation, and sepsis.

6 | CLINICAL PRESENTATIONS, SYMPTOMS, AND DIAGNOSIS

6.1 | How long is the incubation period for mpox, and what are the associated symptoms and potential complications?

The incubation period of mpox infection typically ranges between 5 and 21 days, being the mean incubation period of 9 days.[2,125] The duration of this period varies depending on the transmission route. Thus, the incubation period for contact with mpox through intact skin is approximately 13 days, while contact with broken skin or mucous membranes is generally 9 days.[119,126] It is important to note that some individuals may be contagious 1–4 days before experiencing symptoms.[2] Typically, the initial symptoms of mpox infection are usually flu-like, including fever, chills, headache, muscle pains, fatigue, and sore throat. Upper respiratory symptoms, such as cough, are also common, along with lymph node inflammation, which can include enlarged cervical or submaxillary lymph nodes. Subsequently, a skin rash may appear 1–3 days after the fever has subsided (Box 1). The rash can be itchy or painful and often starts on the face and then spreads to other parts of the body, including the palms of the hands and soles of the feet. Some people may also experience oropharyngeal lesions such as oral ulcers, tonsillitis, and eye symptoms like conjunctivitis and blepharitis.[1–4] However, in the context of the global outbreak of mpox, in over half of the cases, the illness begins differently, and a rash may appear before or at the same time as other symptoms and does not always progress over the body.[4,116]

Symptoms typically are mild and self-limited, and some subjects do not develop any symptoms. They usually last 2–4 weeks, although in cases with a weakened immune system, mpox may cause prolonged illness.[127,128] Additionally, people with low immunity, as well as children and pregnant women, are at higher risk of severe outcomes and death.[4,129,130]

Complications of mpox infections include neurological manifestations (encephalitis or transverse myelitis);[131,132] ocular involvement (conjunctival vesicles, anterior uveitis, keratitis, and corneal ulceration, which can result in blindness);[133] bronchopneumonia; digestive involvement (including difficulty swallowing with dysphagia, vomiting, and diarrhea, causing severe dehydration or malnutrition); cardiovascular complications (that can range from mild transient abnormalities to severe complications, such as myocarditis, congestive heart failure, and arrhythmias); urinary tract inflammation and sepsis. Bacterial superinfected skin lesions may lead to abscesses or severe skin damage such as paronychia, cellulitis, and lymphangitis. When genital and perianal areas are affected, superinfections may lead to cellulitis, balanitis, paraphimosis, and proctitis.[134–136]

While defective skin barrier function has not been strongly correlated with an increased risk of mpox susceptibility, cases of mpox associated with eczema in subjects suffering from atopic dermatitis

(AD) have been described. This condition has been named eczema monkeypoxicum (EM).[137,138] The first EM case was documented in 2022 in a 63-year-old male correctional officer in the USA with a history of AD of the hands, which was managed exclusively through topical treatments. He was employed at a facility where two mpox cases had been confirmed. Notably, he had no documented direct exposure to these infected individuals or their immediate environments, and he also denied other risk exposures to MPXV. The officer developed extensive skin lesions on the hands, elbows, and back induced by clade IIa MPXV that gradually resolved over 3 weeks. It was argued that MPXV infection was probably induced occupationally via fomites in this patient.[137] The second EM case was described in a 28-year-old female with untreated AD of the ears who developed disseminated skin lesions (around 80) induced by MPXV starting in the ears. The mode of transmission of mpox in the patient was unknown since she denied any risk exposures to MPXV.[138] Both reported EM cases suggest that for AD patients, mpox may be contracted not only through direct contact but also via more casual exposures, such as contact with fomites or other indirect transmission routes.[137,138]

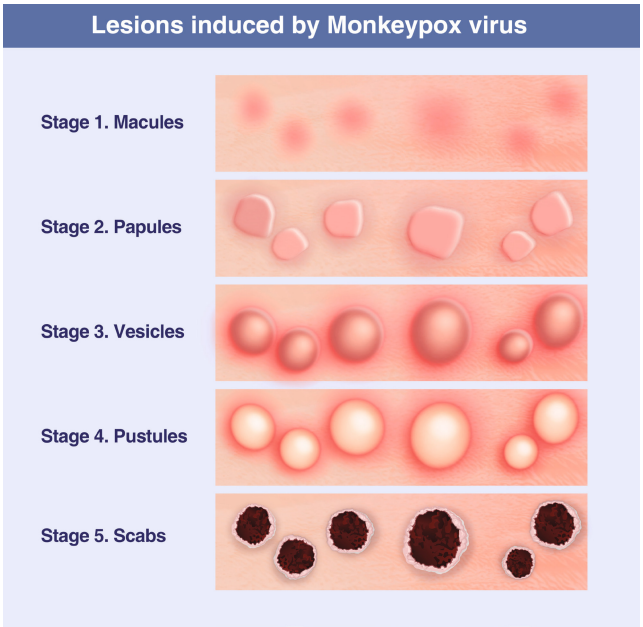

FIGURE 7 Stages of the skin lesions induced by MPXV.

6.2 | What are the typical features of skin lesions caused by MPXV?

The skin lesions caused by mpox typically progress through several stages, each with distinct characteristics (Box 2) (Figure 7).

These lesions often start on the face and then spread to other parts of the body, being the most frequent locations perianal, genital, oral, trunk, and upper and lower extremities, including the palms of the hands and soles of the feet.[2,139–141] The lesions can be painful and itchy and often exist simultaneously in the same development phase. However, in the current outbreak, atypical lesions at different stages of development (asynchronous) and isolated lesions in genital or perineal/perianal areas with no skin involvement in other sites have been described.[4,142]

6.3 | Is a PCR available as a diagnostic tool to detect the novel clade Ib responsible for the 2024 mpox outbreak?

The laboratory test used to diagnose mpox is based on real-time polymerase chain reaction (real-time PCR).[17] Numerous laboratories around the globe have well-established mpox laboratory diagnostics, with over a 100 MPXV laboratory tests receiving official validation, primarily through PCR-based methods. These assays are designed for the specific detection of MPXV or broad orthopoxvirus identification.[143,144] Some real-time PCR protocols are clade-specific, being able to distinguish between clade I (Central African), clade IIa (Western African), and clade IIb (associated with the 2022 outbreak).[145] However, the current 2024 outbreak is associated with the novel clade Ib, which has a deletion in the OPG032 (C3L) gene. Therefore, the already established methods for the MPXV detection are not accurate in the detection of the new variant. In response to this drawback, a new validated real-time PCR protocol has been recently developed for the specific detection of the clade Ib variant.[146] The molecular characterization of the genetic clade of MPXV in the sample specimens through nucleotide sequencing is also a valuable tool for detecting the clade Ib variant.[17]

Antigen and antibody detection methods are not recommended for confirming mpox diagnoses because they do not differentiate among Orthopoxviruses. Additionally, vaccinations with vaccinia-based vaccines may trigger false positives in these tests. Consequently, relying on serological and antigen detection tests for diagnosing mpox is discouraged.[4]

BOX 2 Characteristics of skin lesion stages induced by mpox

- Macules: Flat, pigmented areas on the skin.
- Papules: Elevated bumps that form from macules.
- Vesicles: Tiny fluid-filled blisters.
- Pustules: Pus-filled vesicles.
- Scabs: Pustules that become dry and develop crusts.

6.4 | Which types of samples are appropriate for conducting diagnostic tests for mpox?

Skin lesion specimens are considered the most reliable for PCR-based mpox diagnosis. The preferred samples from the skin lesions are swabs of the lesion surface, exudate, or crusts. The specific

methods and materials for sample collection can differ based on the stage of the rash, such as taking swabs from the surface of active lesions or crusts from healing lesions.[147] It is recommended to take two swabs per lesion from different body locations or from lesions that look distinct from each other and place them in separate tubes. Using invasive procedures such as unroofing or aspiration of lesions or employing sharp instruments before swab collection for mpox testing is unnecessary.[147] Due to the transient nature of viremia relative to the timing of symptom onset, blood samples are not optimal for PCR-based diagnostic testing of mpox.[4] In addition to real-time PCR on skin lesions, throat swabs can be utilized in specific cases, such as individuals with systemic symptoms who have not yet developed skin lesions but are high-risk contacts of confirmed or strongly suspected cases of mpox infection.[17] If the throat swab test returns a negative result, the person must maintain isolation and continue to be monitored as per guidelines from their local health provider. If additional symptoms manifest, reassessment and further testing should be conducted.[148]

6.5 | How are samples collected and handled in accordance with testing procedures?

Laboratories must conduct thorough site-specific and activity-specific risk assessments to identify potential hazards and implement effective mitigation strategies when handling samples from suspected mpox cases. A key component of these strategies includes personal protective measures such as adherence to stringent hand hygiene practices and the use of personal protective equipment (PPE). In that respect, when collecting samples from individuals suspected or confirmed to have mpox, PPE must be worn by personnel trained explicitly in PPE use and sample handling.[147] These protective measures are designed to safeguard the skin and mucous membranes against exposure to MPXV. Moreover, employers should offer vaccination to workers who handle mpox samples. It is also recommended that any practices that may produce infectious aerosols be steered clear. Laboratories should be equipped with the necessary tools and appropriate diagnostic assays and staffed by thoroughly trained personnel. Routine processing of diagnostic mpox specimens should be performed in a Biosafety Level 2 (BSL-2) environment to ensure containment of this pathogen.[149] Specimen manipulation should only occur within a certified Class II Biosafety Cabinet to prevent exposure to potentially infectious aerosols. Working with open vessels on benchtops should be strictly avoided unless specific risk assessments for the site and activity have determined it is safe to do so. Effective management of laboratory mpox waste is another critical aspect. All sharp contaminated objects should be placed in puncture-resistant containers and should be treated as infectious waste. Additionally, all materials, including media, stock solutions, residual samples, and any waste harboring MPXV, must be effectively sterilized before being discarded on-site, with autoclaving being an approved method for this purpose. By the implementation of these comprehensive safety protocols, facilities can significantly reduce the risk of occupational exposure to MPXV.[149]

6.6 | What exclusion criteria are followed in mpox diagnosis?

Cases may be dismissed as confirmed, probable, or suspected cases of mpox under specific circumstances, according to CDC.[150] One primary exclusion criterion is the presence of an alternative diagnosis that fully accounts for the symptoms observed, negating the likelihood of mpox. However, due to the potential for misdiagnosis of the mpox rash with other infections such as herpes or syphilis and the possibility of co-infection with other pathogens, mpox testing is advised for individuals exhibiting a dubious rash, even if they test positive for another pathogen. Furthermore, cases are generally excluded if the affected individuals exhibit symptoms typical of mpox but fail to develop lesions within the initial 5 days following symptom onset. Another significant exclusion factor involves the absence of a positive PCR result for MPXV or Orthopoxvirus from high-quality specimens. This criterion supports excluding a diagnosis when there is no laboratory evidence of the MPXV presence.[150]

7 | MANAGING AND PREVENTING MPOX: EFFECTIVE STRATEGIES

7.1 | What treatment options are currently available for mpox, and which antiviral drugs have proven effective?

Currently, there is no approved treatment specifically for mpox infection. Most patients with mpox experience either asymptomatic or mild symptoms and, therefore, recover without the need for medical intervention.[1–4] However, some patients have presented with severe manifestations of mpox, including ocular infections,[133] neurological complications,[131,132] myopericarditis, and issues related to mucosal lesions in areas such as the mouth, rectum, genitals, and urethra.[134] Additionally, complications can arise from uncontrolled viral spread, particularly in individuals with moderate to severe immunodeficiency, such as those with advanced HIV infection.[127,129,130] Severely immunocompromised patients or those with certain skin conditions, like eczema, are especially at risk for uncontrolled viral dissemination, a severe and potentially life-threatening manifestation of mpox.[4]

Several antiviral agents may effectively treat mpox infections, although their approval for mpox management has been based on animal models. Tecovirimat, also known as TPOXX or ST-246, is a new antiviral drug available for the treatment of mpox. This medication can be administered orally or intravenously and is indicated for certain patients with significant comorbidities, such as immunocompromised individuals, those with atopic dermatitis, or other conditions affecting skin integrity, as well as for children, pregnant women, and breastfeeding mothers.[151] A recent study conducted

in DRC on clade I mpox showed that tecovirimat did not reduce the duration of mpox lesions in children and adults with this clade. However, the overall mortality observed in the study, at 1.7%, was significantly lower than the 3.6% or higher mortality rate reported in cases across DRC.[152] This suggests that patients with mpox can achieve better outcomes when hospitalized and provided with high-quality supportive care. In terms of safety and tolerability, tecovirimat was well tolerated, with no serious drug-related adverse events reported.[152] Further studies are currently underway to assess the effectiveness of tecovirimat.

The STOMP study is investigating the potential benefits of tecovirimat for patients with clade II mpox and those who are immunocompromised or at higher risk of developing severe disease.[153] Additionally, other therapies are being considered for use in combination with tecovirimat or as alternative treatments for MPXV infections in specific situations. Patients experiencing gastrointestinal symptoms, such as vomiting and diarrhea, require oral or intravenous rehydration to manage fluid loss.[154] Other antiviral drugs, such as cidofovir and brincidofovir, are currently being studied. Cidofovir is approved in both the European Union and the United States for the treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome (AIDS).[151] Although there are no definitive data on the effectiveness of cidofovir against mpox in humans, it has shown efficacy against orthopoxviruses in vitro and animal studies. However, its nephrotoxicity limits its use as a first-line treatment. Brincidofovir, on the other hand, was approved in the United States in June 2021 for treating mpox in adults and pediatric patients, including neonates. However, it has not yet received approval in the European Union. While clinical data confirming its effectiveness against mpox are lacking, in vitro and animal studies have demonstrated its efficacy against orthopoxviruses. Finally, the effectiveness of immunoglobulins, which contain antibodies from individuals vaccinated against smallpox, in treating mpox complications remains unknown.

7.2 | What are the guidelines for prescribing antivirals to treat mpox?

CDC continually updates its section on "Mpox Treatment Information for Healthcare Professionals," providing guidance on the latest available medications and important considerations to help healthcare providers determine which patients, based on their comorbidities and clinical characteristics, require specific treatment.[151] A critical aspect to consider is the importance of supportive care,[155] which remains essential in managing mpox cases. This care includes rehydration, either orally or intravenously, to minimize fluid loss, maintenance of hemodynamic stability, supplemental oxygen, symptom management, and treatment of bacterial superinfections of skin lesions. For ocular infections and complications, the use of ocular lubricants, topical antibiotics, and, in some cases, topical antivirals such as trifluridine are recommended. Individuals with compromised immune systems, particularly those living with HIV and having a CD4 count below 200 cells/mm^3, are at higher risk of experiencing a more severe progression of the disease, characterized by increased morbidity and mortality.[156] While the treatment of mpox is primarily symptomatic and supportive, antiviral medications become necessary in more severe or complicated cases.[156]

In June 2022, WHO released the document titled "Clinical Management and Infection Prevention and Control for Mpox: Interim Rapid Response Guidance." This document is intended to offer provisional guidance to clinicians, health facility managers, health workers, and infection prevention and control (IPC) practitioners.[157] It applies to a range of settings, including but not limited to primary care clinics, sexual health clinics, emergency departments, dental practices, infectious disease clinics, genitourinary clinics, maternity services, pediatrics, obstetrics and gynecology, and acute care facilities that handle patients with suspected or confirmed mpox.

In Italy, the Italian Society of Infectious and Tropical Diseases (SIMIT) has released a guideline titled "Vademecum for the Management of Human Monkeypox Virus (MPXV) Infections, Edition 1.0, November 28, 2022."[158] This document outlines a treatment protocol that includes antiviral medications. The primary recommended regimen is tecovirimat 600 mg twice daily for 14 days, with possible dose adjustments for individuals weighing less than 40 kg. The therapy duration may be shortened to 10 days for patients without known immunosuppression. In cases of severe disease or profound immunosuppression, the combination of tecovirimat with cidofovir (CDV) or brincidofovir (BCV) may be considered to prevent the development of resistance to tecovirimat.

Pharmacological treatment is indicated if at least one of the following criteria is met:

1. Mucosal involvement (primarily proctitis, but also oral cavity and conjunctiva).
2. Immunosuppression (including HIV infection classified as stage C by CDC criteria).
3. Bacterial superinfection complications (cutaneous and/or mucosal).
4. Severe or disseminated disease (including persistent symptoms and severe mucosal pain).

For children and individuals weighing less than 13 kg, the use of BCV or CDV may be considered, with CDV being prescribed only if the glomerular filtration rate is above 55 mL/min, proteinuria is less than 1+, and there is no planned co-administration of other nephrotoxic agents. BCV is approved by the US Food and Drug Administration (FDA) but is not authorized by the European Medicines Agency (EMA).

A recent update to the guidelines for healthcare professionals on mpox was published following the latest epidemiological updates from the European Centre for Disease Prevention and Control (ECDC) on August 22, 2024.[159] The updated factsheet for health professionals on mpox was revised to reflect the latest epidemiological data, vaccination prevention, preventive measures, clinical features and sequelae, transmission, diagnostic methods, as well as the

management and treatment of cases. Patients are advised to isolate themselves until the complete resolution of the rash, which indicates the end of infectivity. The treatment of cases is almost exclusively supportive, focusing on alleviating fever, itching, pain and ensuring hydration, including preventing and treating secondary bacterial infections.

7.3 | What precautions should individuals in close contact with infected patients follow to prevent transmission?

The transmission of mpox between humans primarily occurs through close contact with an infected individual. The term "close contact" for mpox is defined as any individual exposed to an infected person during the period between the onset of symptoms and the complete healing of the rashes. High-risk exposure is also described as direct contact with body fluids or lesion material, needle injuries, contact with contaminated materials such as linens and clothes, and prolonged face-to-face contact without appropriate personal protective equipment.[160–164]

Individuals who have been exposed to MPXV should be monitored daily for a period of 21 days following the last exposure. Asymptomatic individuals do not require isolation; however, they should be monitored for symptoms of mpox, including a skin rash or lesions, chills, headache, fever, sore throat, fatigue, and lymphadenopathy.[161–164] Additionally, daily body temperature monitoring is recommended at least once or twice per day. To prevent the masking of early signs of mpox infection, such as fever, it is essential to avoid using acetaminophen or ibuprofen. It is recommended that individuals undergoing monitoring for mpox infection adhere to good hygiene practices, observe respiratory etiquette, and engage in safe sexual behaviors (e.g., the use of condoms) throughout the monitoring period (Box 3).[162]

In the event of symptoms, the subject should be placed on empiric isolation precautions for mpox and should contact the healthcare provider. Healthcare professionals who have had occupational exposure to patients with mpox or potentially contaminated materials may continue to work if asymptomatic but should avoid providing care to patients at high risk for severe mpox disease, such as pregnant women, newborns, and immunocompromised patients.[161,162]

BOX 3 Recommendations for individuals in close contact with infected patients

- Daily monitoring for mpox symptoms over 21 days.
- Daily body temperature monitoring (1–2 times/day) is recommended.
- Acetaminophen or ibuprofen should be avoided to prevent masking early mpox symptoms.
- Good hygiene, respiratory etiquette, and safe sex practices (e.g., condom use) should be maintained during mpox monitoring.
- Isolation is not necessary unless symptoms develop.
- If symptoms emerge, empiric isolation for mpox should be initiated, and healthcare provider should be contacted.

7.4 | What are the available vaccines for mpox?

From the outset of the current epidemic, vaccination has been recognized as a vital complement to key public health measures. On July 22, 2022, a non-replicating third-generation smallpox vaccine based on a live attenuated virus from the Ankara strain (MVA-BN) was introduced to the market under two main brand names: Imvanex and Jynneos.[165] Although there are minor differences in production processes and quality specifications between these two vaccines due to varying data sets linked to different regional marketing authorizations, these variations do not compromise the final quality of the vaccine.[165] Imvanex has been registered in Europe by EMA since 2013, initially as a vaccine for smallpox.[166] As of July 22, 2022, it is also registered for use against mpox.[167] Jynneos was first approved by the U.S. Food and Drug Administration (FDA) on September 24, 2019, to prevent both smallpox and mpox.[168] This approval marked a significant step in the availability of vaccines capable of addressing both smallpox and mpox, reinforcing the importance of vaccination as a critical tool in managing public health threats.

To ensure protection against mpox, Jynneos and Imvanex must be administered as a subcutaneous injection (0.5 mL) with a two-dose regimen. The second dose should be administered at least 28 days after the first as a primary vaccination for individuals not previously vaccinated against smallpox. Due to limited supplies of Jynneos in the EU/EEA during the summer of 2022, the EMA's Emergency Task Force issued a recommendation in August 2022 supporting antigen-sparing vaccination strategies through intradermal administration (on the volar surface of the forearm) of a fractional dose.[169] Evidence indicated that the lower intradermal dose of the vaccine had comparable humoral immunogenicity to the standard subcutaneous dose.

7.5 | What are the recommendations and guidelines for the preventive usage of vaccines in mpox?

WHO has established guidelines for the use of vaccines in response to the global mpox outbreak.[170] The primary goal is to control the spread of the virus through public health measures like surveillance, contact tracing, and isolation.[170] While mass vaccination is not recommended, WHO advises the judicious use of vaccines, particularly in high-risk groups. For post-exposure prophylaxis (PEP), vaccination

is recommended within 4 days of exposure. For pre-exposure prophylaxis (PrEP), it is suggested for health workers and laboratory personnel at high risk of exposure.

The CDC currently recommends the mpox vaccine, administered as a series of two doses given 28 days (4 weeks) apart.[171] For individuals with sexual risk factors for mpox who have not been diagnosed with mpox during the ongoing outbreak or have not yet received both doses of the mpox vaccine, routine vaccination is recommended. Additional doses beyond the initial two are not currently advised.[171] For those with occupational risk of exposure to orthopoxviruses (such as certain research laboratory workers), a booster vaccination is recommended every 2–10 years, depending on the nature of the work performed.[171] Vaccinated individuals should continue to take precautions to protect themselves from infection by avoiding close, skin-to-skin contact, including intimate contact, with anyone infected with mpox.[171]

In the EU/EEA, the Imvanex vaccine is authorized to protect adults from mpox and diseases caused by the vaccinia virus.[172] Upon authorization, data from human and animal studies suggested that a single dose of MVA-BN might provide rapid protection against mpox, with the second dose mainly serving to extend the duration of immunity.[173] A single booster dose may be considered for individuals previously vaccinated against smallpox, mpox, or vaccinia viruses, although there are insufficient data to determine the optimal timing for booster doses. The safety profile of MVA-BN is favorable, with generally mild to moderate side effects. In contrast, older-generation smallpox vaccines, which have more significant side effects, are not authorized by EMA. Due to limited supplies of Imvanex in the summer of 2022, the EMA's Emergency Task Force recommended the use of intradermal delivery of a fractional dose (one-fifth of the standard subcutaneous dose), which was shown to have comparable immunogenicity to the full subcutaneous dose.[169] In Italy, the Ministry of Health's Circular from August 5, 2022, recommends the MVA-BN vaccine as pre-exposure prophylaxis for laboratory workers at risk of orthopoxvirus exposure and men who have sex with men, following specific risk criteria.[174]

Countries have prioritized preventive vaccination for high-risk groups, such as gay, bisexual, and transgender individuals who have sex with men, based on epidemiological and behavioral criteria such as the frequency of sexual encounters and participation in group sex events. In the United States, the CDC recommends vaccination for individuals exposed to mpox, those with recent sexual partners diagnosed with mpox, and those at high risk of occupational exposure to orthopoxviruses.

7.6 | What are the specific contraindications for mpox vaccines?

The only absolute contraindications to the MVA-BN mpox vaccine are a history of anaphylaxis after a prior dose of any MVA-BN mpox vaccine or a severe allergic reaction to any of its components or residual traces.[175] Additionally, the MVA-BN mpox vaccine has not been formally studied in pregnant or breastfeeding women, although limited animal studies have not identified any vaccine-related fetal malformations.[176] Regarding precautions, a study conducted in the United States found that vaccine effectiveness (VE) among immunocompromised individuals was 70.2%, compared to 87.8% in immunocompetent participants.[177] Despite this difference, there have been no reported safety concerns or issues with vaccine efficacy in immunocompromised populations, including recipients of hematopoietic stem cell transplants.[178] Clinical data on the use of the MVA-BN vaccine in individuals with HIV infection are limited.[175] However, the vaccine appears to be well tolerated in these populations, showing no adverse effects on viral load or CD4 cell counts.[179] In the case of antibody-deficient patients, the humoral response is compromised, potentially reducing VE. However, cellular immunity may still be partially intact, potentially providing some level of protection. Currently, the VE for antibody-deficient conditions is very limited. The CDC's Advisory Committee on Immunization Practices (ACIP) recommends the MVA-BN mpox vaccine for populations at risk of mpox infection, regardless of their immunocompromised status.[177] However, further research is needed to better understand the vaccine efficacy in individuals with antibody deficiencies. Regarding individuals with atopic dermatitis, local adverse reactions following the MVA-BN vaccine appear to be more common according to some studies in the literature and pharmacovigilance data.[180] However, these adverse events are generally mild and do not compromise the overall safety profile of the vaccine.[181]

7.7 | Do smallpox vaccines offer protection against MPXV?

During the global smallpox eradication campaign, vaccination provided significant cross-protection against mpox infection.[182] In April 2022, WHO formed a dedicated working group under the Strategic Advisory Group of Experts (SAGE) on Immunization to advise on the deployment of vaccines for mpox.[183] This group was also assigned to revise and update the 2013 guidelines regarding the use of smallpox vaccines. While vaccination against MPXV infection has relied on smallpox-specific vaccines, those targeting MPXV directly are currently in experimental development. Two studies conducted in Zaire compared secondary infection rates of MPXV among close contacts who were unvaccinated and those who had previously received smallpox vaccination as part of the eradication effort. In the first study, the overall attack rate of secondary MPXV infection among individuals with a history of smallpox vaccination was 1.1%, compared to 7.4% in those who had not been vaccinated.[16] In the second study, which examined 2278 close contacts of 245 mpox patients from 1981 to 1986, the attack rate of secondary infection among unvaccinated close contacts was 7.47%. In contrast, it was only 0.96% among those who had been vaccinated.[184]

A comprehensive meta-analysis and systematic review published in 2024 evaluated the safety, efficacy, and protection of the mpox vaccine.[185] The findings indicated that the vaccine has a good safety profile, with only mild side effects reported. Additionally, the efficacy data gathered from 11 published studies revealed that among 13,505 vaccinated participants compared to 19,786 unvaccinated participants, the risk of MPXV infection was reduced by 54% with vaccination against smallpox compared to those without vaccination. The actual efficacy of this antibody response in protecting against MPXV infection remains uncertain, highlighting the need for further research to understand the vaccine's protective capabilities better.[182]

To date, for individuals who were previously vaccinated against smallpox and are now in high-risk groups for whom mpox vaccination is recommended, a booster dose of MVA-BN has been advised. Moreover, according to various studies in the literature, a single dose of MVA-BN has proven to be highly protective against symptomatic mpox disease among high-risk GBMSM (gay, bisexual, and other men who have sex with men).[186] This makes it a valuable tool for controlling mpox outbreaks when rapid protection is required. However, the long-term protection offered by a single dose needs further investigation.[187] In situations where the number of individuals at high risk of infection exceeds the available vaccine supply, prioritizing the administration of initial doses may be beneficial.

7.8 | How long does the immunity provided by the vaccines last?

The duration of protection the smallpox vaccine provides against MPXV infection is not yet well defined. However, long-term follow-up studies on individuals vaccinated against smallpox have shown that neutralizing antibody responses against the vaccinia virus can remain stable in the blood for many decades and, in some cases, even for a lifetime.[182] According to a recent study published in The Lancet, nine countries reported data on individuals with confirmed mpox via PCR after either a previously documented infection or vaccination between May 11, 2022, and June 30, 2023.[188] Among the 37 infected subjects, those with natural immunity from prior infection experienced a shorter illness duration and less mucosal disease during reinfection compared to their initial infection. Post-vaccination infections were characterized by fewer lesions, minimal mucosal involvement, and minimal need for pain relief. The study concludes that the clinical features and outcomes of recurrent infections and infections following vaccination appear less severe than cases reported in 2022. Specifically, compared to the 2022 case series, individuals in this study exhibited fewer confluent lesions, reduced mucosal involvement, decreased need for analgesics, and fewer hospitalizations. While natural immunity and vaccine-induced immunity do not offer complete protection against mpox infection, in this small cohort, both the duration and severity of the illness seem to be diminished.

According to the Advisory Committee on Immunization Practices (ACIP) recommendations on Orthopoxvirus vaccines (smallpox and mpox), maximum immunity is achieved 14 days after the second dose of the vaccine. The administration of additional vaccine doses (beyond the two recommended doses) is not currently advised for most individuals. However, for those at risk of occupational exposure to orthopoxviruses (e.g., certain research laboratory workers), booster doses are recommended every 2 to 10 years, depending on the nature of their work.[189] While there are no definitive data in the literature regarding the duration of protection provided by these vaccines,[169] booster doses may be indicated based on risk assessment. The possibility of administering a single-dose regimen is increasingly being studied, though the duration of protection for such a regimen is not yet fully understood.[186,190,191]

8 | POTENTIAL CAUSES AND OUTCOMES OF THE RECENT MPOX OUTBREAKS

8.1 | Could the 2022 and 2024 mpox outbreaks be connected to factors like deforestation and climate change?

For a pathogen to produce a zoonotic outbreak, there should be an alignment of often complex and dynamic conditions—including ecological, epidemiological, immunological, and behavioral conditions.[192] Intact ecosystems provide the first line of defense against new pandemics because they strengthen the first three barriers to spillover (minimizing distribution overlap, host stress, and human exposure) and hence decrease the likelihood that the conditions for spillover occur or align.[193] Amplifying drivers of zoonotic diseases thus include landscape alterations and climate hazards induced by climate change.

In 2022, WHO clearly linked the MPXV outbreak to climate change, explained by the shrinking space between human communities and wildlife habitats and by rising levels of ecological fragility and climate stress, which is changing both animal and human behavior. Since 2022, global warming and climate change have increased the frequency and intensity of wildfires, sand and dust storms, thunderstorms, and heat waves—with concomitant increases in air pollution, heat stress, and flooding.[12] A study performed in 2022 examined the changes in mpox cases over time while assessing the meteorological characteristics that could impact mpox.[194] Temperature, relative humidity, and surface pressure positively impacted mpox cases, while dew/frost point, precipitation, and wind speed showed a significant negative impact. Overall, there was a significant correlation with rising mpox cases.

A recent workshop discussed six steps to prioritize climate-sensitive zoonoses based on a structured approach to defining criteria for climate sensitivity.[195] A new interactive expert elicitation interface was proposed to facilitate data collection and real-time

visualization of prioritization results, allowing for a structured decision-making support process when allocating limited financial and personnel resources to enhance preparedness and response to zoonotic diseases amplified by climate change.

8.2 | Could demographic shifts have played a role in the 2022 and 2024 mpox outbreaks?

Natural, geographical barriers have historically limited the spread of communicable diseases. This is no longer the case in today's interconnected world, paired with its unprecedented environmental and climate change, emphasizing the intersection of evolutionary biology, epidemiology, and geography.[196] The translocation of pathogens and their vectors is closely connected with human mobility, migration, and the global transport of goods. The destruction of natural ecosystems, coupled with low income and socioeconomic status, increases the transmission probability of neglected tropical and zoonotic diseases. During 2012–2021, the volume of international travel reached record highs and lows. This period also was marked by the emergence of large outbreaks of multiple infectious diseases (e.g., Zika virus, yellow fever, and COVID-19).[197] After restrictions were lifted, the unprecedented ease and increased frequency of travel may result in a dangerous global spread of infectious diseases. Active surveillance for infectious diseases among travelers can serve as sentinel systems for new or emerging pathogens.

8.3 | Has the enhancement of surveillance and reporting systems led to the identification of more mpox cases?

AI-based models in the context of increased surveillance integrating environmental and socioeconomic predictors of zoonotic disease spread have definitely helped in the early identification and isolation of mpox cases.[198] However, there is also a real increase in vulnerable individuals due to the steady increase of environmental stressors such as microbial and epithelial barrier dysregulation, increased hygiene, refined diet, and air pollution, increasing the likelihood of susceptibility to disease and exaggerated inflammatory responses.[12,199]

8.4 | Are we experiencing a rise in zoonotic diseases, and what might be the potential impacts of the ongoing mpox outbreaks?

A recent analysis that excluded the SARS-CoV-2 pandemic showed that the number of spillover zoonotic events and associated deaths have been increasing by 4.98% (confidence interval [CI]95% [3.22%; 6.76%]) and 8.7% (CI 95% [4.06%; 13.62%]) annually, respectively.[200] This paper underscores the importance of immediate and appropriate preventive measures (timely preparedness and proactive control strategies) with utmost priority against zoonotic diseases, including awareness-raising programmes, discovering and formulating effective vaccine candidate(s), prophylaxis and therapeutic regimes, and management strategies. The ongoing mpox outbreaks are expected to impact vulnerable populations profoundly. They might entail shortages in the accessibility to regular checks for chronic diseases or medication availability due to a shift of limited resources toward containment of the outbreak.

Although preparedness and response have received significant focus, prevention remains largely absent from global conversations. A special focus on increasing resilience in vulnerable populations is warranted as a public health initiative.[201–203] In addition, ecological countermeasures targeting the root causes of zoonoses are urgently needed.[204] By protecting and restoring the wildlife habitat and by mitigating wildlife-human interactions, these measures are strategically designed to increase the resilience of reservoir host populations, reduce stress and likelihood of viral shedding, prevent distributional shifts, and protect vulnerable human communities.

9 | CONCLUSION

The resurgence of mpox in 2024, driven by the emergence of a new, more transmissible variant, underscores the ongoing vulnerability of global health systems to zoonotic diseases. Despite advances in diagnostics and vaccines, the rapid spread of clade Ib, within Africa and probably across borders, has reignited concerns about the readiness and coordination of international responses. The higher CFR compared to the 2022 outbreak highlights the increased threat, particularly in regions with fragile healthcare infrastructure. As climate change continues to disrupt natural ecosystems and human-wildlife interactions, the conditions for zoonotic spillover events will only intensify. This outbreak not only demands immediate containment efforts but also serves as a critical reminder of the broader, long-term impacts of ecological degradation, socioeconomic inequality, and global health inequities. The urgency of a coordinated, sustained response is apparent: efficient responses to current threats and preventive measures for future outbreaks demand robust support from society and institutions. In a context characterized by concerns about drug supply shortages and the emergence of resistance, researchers are intensifying efforts to identify new therapeutic targets and treatment options for mpox. The rising resistance to existing medications necessitates urgent innovation in pharmaceutical research to develop more effective and sustainable treatments for this disease. The scientific community is actively exploring new molecules and mechanisms of action that can enhance clinical responses in patients affected by this condition. It is crucial to initiate clinical studies that allow for the evaluation of the efficacy and safety of these new treatments, particularly in vulnerable populations, such as those who are immunocompromised. Establishing clear clinical guidelines and conducting assessments of the long-term response to existing antiviral treatments are essential to ensure adequate and timely management of mpox.

AUTHOR CONTRIBUTIONS

BC and CAA conceptualized the manuscript, designed its structure, coordinated the writing process, and handled the editing. All authors contributed by writing significant portions of the manuscript and collaborated in the final editing of the document.

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CONFLICT OF INTEREST STATEMENT

CAA has received research grants from the Swiss National Science Foundation, European Union (EU CURE, EU Syn-Air-G), Novartis Research Institutes, (Basel, Switzerland), Stanford University (Redwood City, Calif), Seed Health (Boston, USA) and SciBase (Stockholm, Sweden); is the Co-Chair for EAACI Guidelines on Environmental Science in Allergic diseases and Asthma; Chair of the EAACI Epithelial Cell Biology Working Group is on the Advisory Boards of Sanofi/Regeneron (Bern, Switzerland, New York, USA), Stanford University Sean Parker Asthma Allergy Center (CA, USA), Novartis (Basel, Switzerland), Glaxo Smith Kline (Zurich, Switzerland), Bristol-Myers Squibb (New York, USA), Seed Health (Boston, USA) and SciBase (Stockholm, Sweden); and is the Editor-in-Chief of Allergy. MA has received research grants from Swiss National science Foundation, Bern; research grant from the Stanford University; Leading House for the Latin American Region, Seed Money Grant. She is in the Scientific Advisory Board member of Stanford University-Sean Parker Asthma Allergy Center, CA; Advisory Board member of LEO Foundation Skin Immunology Research Center, Kopenhagen; and Scientific Co-Chair of World allergy Congress (WAC) Istanbul, 2022, Scientific Programme Committee Chair, EAACI. JV reports speaker and consultancy fees in the past 5 years from Astra Zeneca, HpVac, L'Oréal, Novartis, Sanofi, Thermo Fisher Scientific, and travel expenses reimbursement from Stallergènes for an international meeting, outside the submitted work. The other authors have no conflict of interest within the scope of the submitted work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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