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Epidemiology-based analysis of the risks and elimination strategies of the monkeypox outbreak in 2022

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ABSTRACT

Monkeypox, caused by monkeypox virus, has spread unprecedentedly to more than 100 countries since May 2022. Here we summarized the epidemiology of monkeypox through a literature review and elucidated the risks and the elimination strategies of this outbreak mainly based on the summarized epidemiology. We demonstrated that monkeypox virus became more contagious and less virulent in 2022, which could result from the fact that the virus entered a special transmission network favoring close contacts (i.e., sexual behaviors of men who have sex with men) and/or the possibility that the virus accumulated a few adaptive mutations. We gave the reasons to investigate whether cattle, goats, sheep, and pigs are susceptible to monkeypox virus and whether infection of monkeypox virus could be latent in some primates. We listed six potential scenarios about the future of the

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outbreak (e.g., the outbreak could lead to endemicity outside Africa with increased transmissibility or virulence). We also listed multiple factors aiding or impeding the elimination of the outbreak. We showed that the control measures strengthened worldwide after the World Health Organization declared the outbreak a public health emergency of international concern (PHEIC) could well control but could not eliminate the outbreak in 2022. We clarified eight strategies, i.e., publicity and education, case isolation, vaccine stockpiling, risk-based vaccination or ring vaccination, importation quarantine, international collaboration, and laboratory management, for the elimination of the outbreak.

KEYWORDS

Monkeypox, risk, elimination, epidemiology, outbreak, prediction

1 INTRODUCTION

Monkeypox (MPX) is akin to smallpox and is caused by monkeypox virus (MPXV). MPXV, which circulated in some African countries before 2022, has spread unprecedentedly to more than 100 countries or territories, and more than 68,000 human cases with 26 deaths have been confirmed since May 1, 2022 (Figure 1).[1-6] The World Health Organization (WHO) declared on July 23, 2022 this multi-country MPX outbreak, which is abbreviated as the Outbreak/2022 below, a public health emergency of international concern (PHEIC).[2]

MPXVs are typical poxviruses with large brick-shaped enveloped virions and a double-stranded DNA genome. MPXVs constitute the species *MPX virus* and share the same genus *Orthopoxvirus*, subfamily *Chordopoxvirinae*, and family *Poxviridae* with *Abatino macacapox virus*, *Akhmeta virus*, *Camelpox virus*, *Cowpox virus* (CPXV), *Ectromelia virus*, *Raccoonpox virus*, *Skunkpox virus*, *Vaccinia virus* (VACV), *Variola virus* (VARV, the etiology of smallpox), *Taterapox virus*, and *Volepox virus*.[7]

Here we summarized the epidemiology of MPX through a literature review and elucidated the risks and elimination strategies of the Outbreak/2022 mainly based on the summarized epidemiology.

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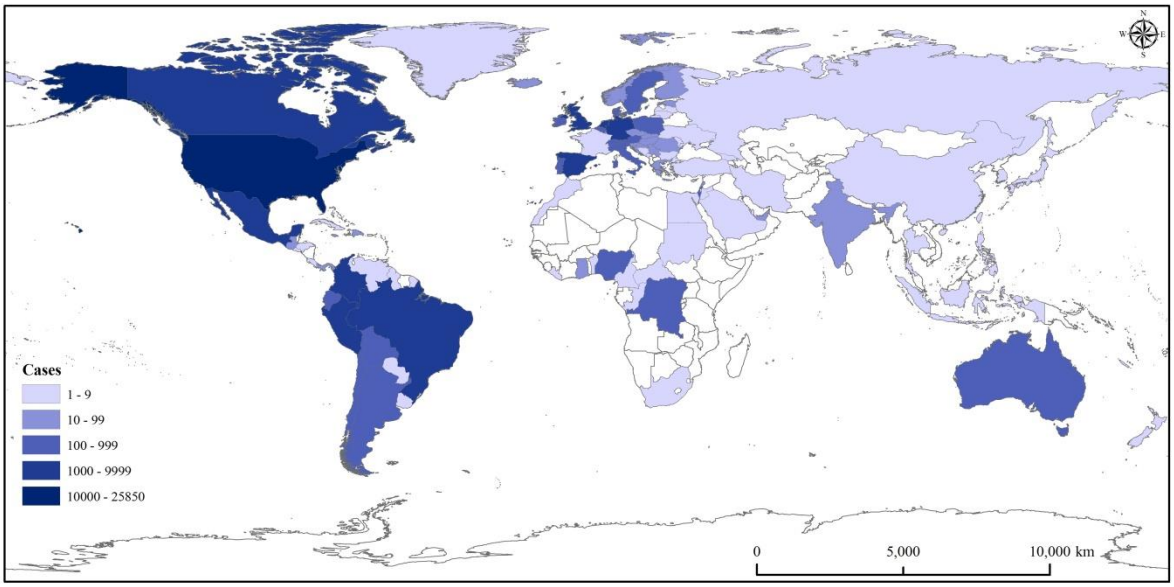

FIGURE 1 Distribution of the cumulative confirmed human monkeypox cases in 2022 as of September 25, 2022 as per the data from the CDC.[3]

2 EPIDEMIOLOGY OF MPX

In temporal and spatial distribution, MPX is endemic in central and western Africa. MPXV and MPXV infections in monkeys were first reported in 1959.[1] MPXV infections in humans, which were first identified in 1970, increased significantly in endemic African regions in recent decades,[9] likely due to the decline of population immunity against smallpox with the cessation of smallpox vaccination in the 1980s.[10] Human cases are often found close to tropical rainforests, where there are animals that carry the virus.[2,8] In recent years, thousands of humans have been infected with MPXV annually in the endemic African regions,[5] and a few imported human cases outside Africa were identified after 2017.[9] A small-scale autochthonous human outbreak occurred in the USA in 2003.[11] As of September 30, 2022, the majority of confirmed human cases (60,713/68,428; 88.73%) in the Outbreak/2022 were reported from some countries in North America, South America, and Europe, including the USA (25,850), Brazil (7,687), Spain (7,147), France (3,999), the United Kingdom (3,635), Germany (2,625), Peru (2,480), Colombia (2,042), Mexico (1,627), and the Netherlands (1,223) (Figure 1).[3]

In host distribution, MPXV can infect various mammals, including rodents (e.g., squirrels, rats, mice, diant-pouched rats, dormice, Gambian giant rats, chinchillas, marmots, groundhogs, prairie dogs), primates (e.g., monkeys, apes, humans), carnivores (e.g., dogs), lagomorphs, and insectivores (e.g., hedgehogs, shrews).

[2,3,12-14] Because MPXV can infect various species of mammals, it could infect cattle, goats, sheep, and pigs. This possibility is supported by an experiment which showed that MPXV replicated in pig skin.[15]

In clinical epidemiology, the incubation period in humans is 5–21 days, and symptoms last 2–4 weeks.[2,3,9] Early symptoms of infected humans include fever, headache, fatigue, and muscle pains, like influenza.[2] Typical skin lesions (rashes) usually appear on the face, then on the trunk, and then on other sites (e.g., hand palms).[2,3] Many male cases in the 2022 MPX outbreak presented with genital and peri-anal lesions.[3] Patients can encounter secondary infections, pneumonia, encephalitis, sepsis, and vision impairment.[2,16] Some infected animals and humans are asymptomatic.[6,17] For example, three human MPX cases in Belgium identified in 2022 were asymptomatic.[17] Animal experiments suggested that infection routes affect clinical severity. For example, it was found that nasal inhalation is more fatal than other inoculation routes to white rats, CAST/EiJ mice, and Prairie dogs.[13,18,19] This is possibly because inflammation is more dangerous in the lungs than in other organs.[20] Most human MPX cases before 2022 occurred in children in the endemic regions,[9] but most human cases in the Outbreak/2022 were young males unvaccinated against smallpox.[3] For example, of the first 23,667 confirmed human MPX cases in the USA in the outbreak_2022, 0.177% were <16 years old, 88.157% 16–65 years old, 0.558% >65 years old, 94.64% were men, 2.20% women, 2.17% transgender women, 0.30% trangender men, 0.69% another sex/gender, 90.337% ≤50 y/o (usually unvaccinated against smallpox as smallpox vaccination terminated in the USA in 1972), and 9.663% >50 years old (usually vaccinated against smallpox vaccines).[3]

In phylogenetic distribution, MPXVs were classified into Clades I and II.[2,6,9] Clade I (formerly designated as ‘Central African’ or ‘Congo Basin’ clade) circulates in central Africa (Cameroon, the Democratic Republic of the Congo (DRC), and Central African Republic, Gabon, Republic of the Congo). Clade II (formerly designated ‘West African’ clade) mainly circulates in western Africa (Benin, Cameroon, Cote d'Ivoire, Liberia, Nigeria, Sierra Leone). MPXV could originate 3500 (95% HPD 2200–5400) years ago, and Clade II MPXV could originate about 600 (95% HPD 300–1000) years ago.[21] Clade II includes Clades IIa and IIb and that they likely diverged in the 1970s.[22] Furthermore, MPXVs possibly originated from

some cowpox viruses and that three lineages of MPXVs within Clade IIb circulated in 2022.[22] Two MPXVs, respectively similar to the two MPXVs exported from Nigeria to the USA in 2021, evolved into two lineages and sparked the large-scale outbreak in 2022, after their unknown evolutionary and epidemiological journeys, possibly in Nigeria, the USA, or other countries before May 2022.[22] Of known orthopoxviruses except some CPXVs, VACVs are the closest in phylogenetics to MPXVs, and vice versa.[22]

In transmission routes, MPXVs spread among animals and humans through three routes.[2,3,6,9,23]: (1) direct close contact (e.g., sexual activity, biting) with infected humans or animals or their wounds, meat, blood, body fluids, or virus-contaminated items; (2) inhalation of respiratory droplets; (3) vertical transmission during pregnancy (Figure 2A). In the Outbreak/2022, MPXV mainly circulates in men who have sex with men (MSM) through sexual behaviors,[2-4] and a human with prolonged seminal viral shedding was identified.[24]

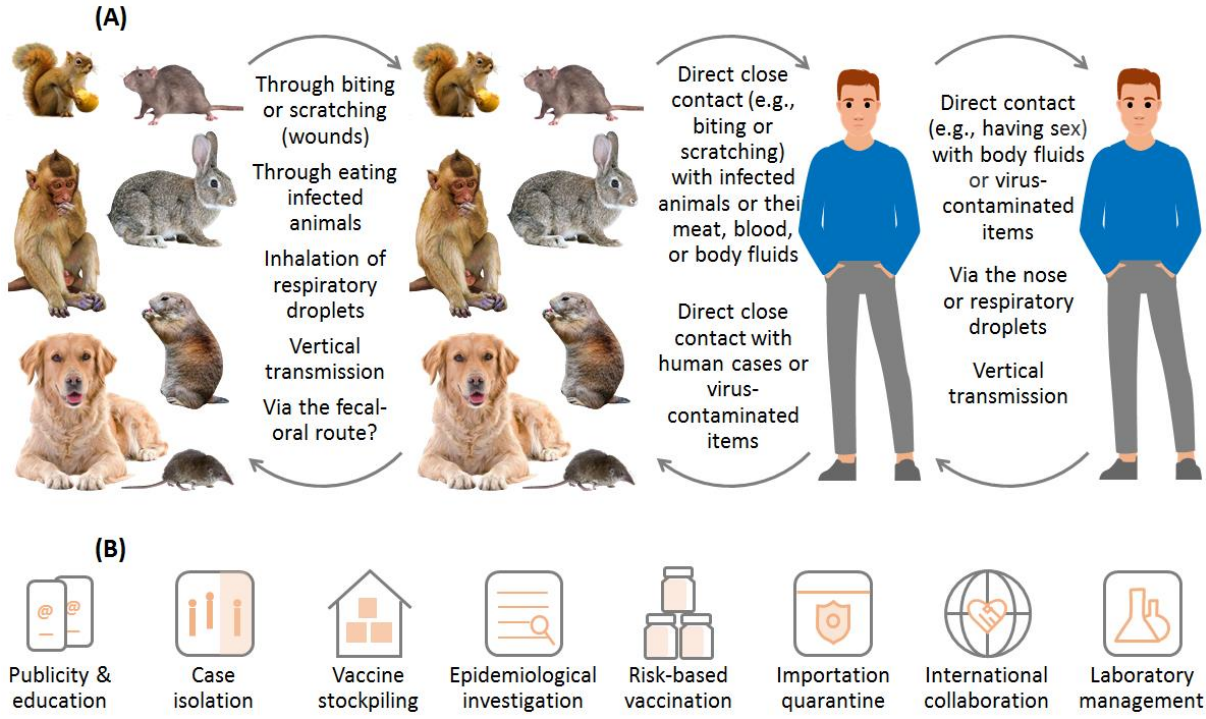

FIGURE 2 Transmission routes of MPX in animals and humans (**A**) and the strategies to block the transmission (**B**).

In infection courses, usually MPXV infection is assumed to be transient, but we suspect that the infection in primates could sometimes be latent, as suggested by

two studies. One was in 1958 in Denmark where MPX occurred in two batches of cynomolgus monkeys only when they had been transported to Copenhagen for 51 and 62 days.[1] The other was in 1961 in the USA where MPX occurred in a cynomolgus monkey only after the monkey had been maintained in the same room for 11.5 months and the monkey was irradiated 45 days before the onset of MPX.[25]

In contagiousness, MPX has become more contagious in humans in recent decades in their endemic regions, because in the 1970s and 1980s, more than 70% of human cases were infected via the animal-to-human route, and in recent years, more than 70% of human cases were infected via the human-to-human route.[9] Nevertheless, the reproduction number (R_0) value of MPXV before 2022 was less than 1.0,[6,9] because many events of human-to-human transmission terminated naturally in endemic regions. However, mathematically, this value should be >1.0 in the Outbreak/2022 before the outbreak was declared a PHEIC by the WHO with the rapid increase in human cases lasting for months (Figure 3). For example, the R_0 value was 1.82–3.26 among MSM in Italy.[26] This suggests that MPXV is more contagious in the Outbreak/2022 than before, which will be discussed below.

In the case fatality rate (CFR), we assumed the outcome of a human MPX case is known on the 21st day after the case was reported.[2-4] Then, the outcomes of the first 52,994 human cases confirmed before September 5, 2022 were known on September 26, 2022 (26 deaths and 52,968 recoveries). Therefore, the CFR of the Outbreak/2022 was approximately 0.049%. This value is much lower than the CFRs of smallpox (approximately 30%), Clade I (approximately 3.6%) before 2022, and Clade II (approximately 10.6%).[9] The significant increase in the R_0 value and the significant declination in the CFR of MPX in 2022 could result from the fact that the virus entered a special transmission network favoring close contacts (i.e., sexual behaviors of MSM) outside Africa.[27] They also could result from the possibility that MPXV accumulated a few adaptive mutations in 2022.[28]

3 RISK OF THE OUTBREAK/2022

In risk factors, as per the epidemiology of MPX elucidated above, endemic countries, international travel, importation of mammals, humans unvaccinated with smallpox vaccines, men who have sex with men, crowded parties, close contact with infected humans, family members of infected humans, rubbish of infected

humans, healthcare workers in affected regions, vaccine unavailability, squirrels, rodents, non-human primates, pet animal markets or traders, and zoos are all risky for the transmission of MPX.[1-6,8-19] Forest regions, particularly those with squirrels and oil palms, were positively associated with annual MPX incidence.[8,29]

In future prediction, Figure 3 showed that, before the WHO declared the Outbreak/2022 a PHEIC on July 23, 2022, the counts of global weekly new MPX cases increased rapidly, and the counts declined rapidly after August 8, 2022 (i.e., 16 days or within one maximum incubation period after the declaration). Therefore, the control measures strengthened worldwide after the declaration could have been highly effective to control the outbreak in 2022. However, non-linear regression of the counts from August 8, 2022 to September 19, 2022 suggested that this outbreak could not be eliminated before 2023 if the control measures were not be further strengthened.

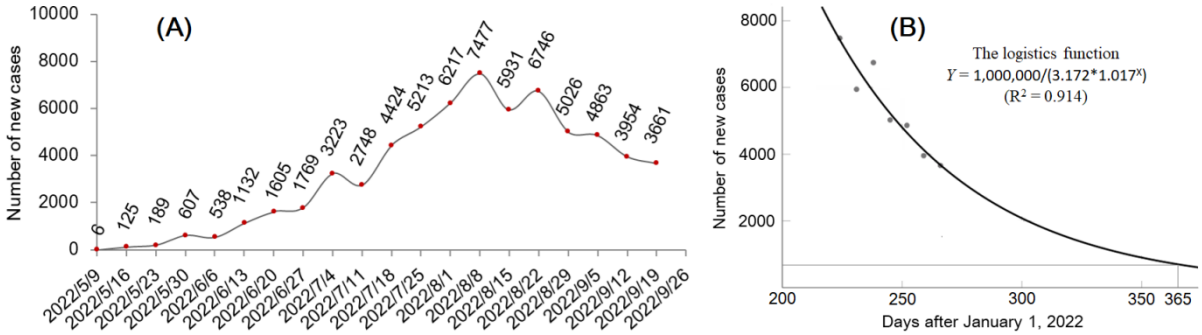

FIGURE 3 Tolls of global new confirmed human MPX cases per week in the Outbreak/2022 (**A**) and a non-linear regression of the tolls from August 8, 2022 to September 19, 2022 (**B**), as per the data from the WHO.[30] The regression was performed using the software tool SPSS (version 23.0). The logistic regression equation was selected because its R^2 value was higher than the R^2 values of other curvilinear regression equations. This regression method is classical for prediction and is based on a single available parameter that represents the effects of multiple factors. This method does not require other assumed or detected parameters. The R^2 of the logistic regression equation was relatively high (0.914), which suggests that the equation is relatively reliable.

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In future prediction, the Outbreak/2022 could exhibit one of the potential scenarios listed in Table 1, relying on the implemented control measures and the genomic changes of MPXV. In scenarios A–D, the Outbreak/2022 will be eliminated outside Africa before the case count reaches 300,000, 1,000,000, 10,000,000, and >10,000,000, respectively. In scenarios E and F, the Outbreak/2022 becomes endemic outside Africa without or with increased transmissibility or virulence. Scenarios D–F could represent a disastrous pandemic. Zoonotic scenario F with natural wildlife reservoirs could be more intractable than smallpox, which circulated exclusively in humans without natural reservoirs. Under scenario F, almost all people worldwide who have not been vaccinated against smallpox should be vaccinated against MPX, which could cost approximately 13 billion USD (0.13 billion newborns/year multiplied by 50 USD/dose and 2 doses/newborn) each year worldwide.

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TABLE 1 Future potential scenarios, relevant factors, and elimination strategies of the monkeypox outbreak in 2022

Future potential scenarios	A: elimination outside Africa with <300,000 cases totally
	B: elimination outside Africa with <1,000,000 cases totally
	C: elimination outside Africa with <10,000,000 cases totally
	D: elimination outside Africa with >10,000,000 cases
	E: endemicity outside Africa without increased transmissibility or virulence
	F: endemicity outside Africa with increased transmissibility or virulence
Factors useful to eliminate the outbreak	The control measures have been strengthened worldwide after the WHO declared the outbreak a PHEIC on 23 July 2022
	Most monkeypox infections in humans are likely self-restricted
	Identification of suspected monkeypox infections is relatively easy
	Monkeypox vaccination and infections usually lead to robust immunity
	Monkeypox virus mutates relatively slowly
	Monkeypox virus spreads relatively slowly
	Monkeypox vaccines have been ready for mass production
	The global weekly new monkeypox cases have been rapidly declining
Factors impeding the elimination of the outbreak	Monkeypox virus has infected too many people in many countries
	Monkeypox virus can infect various species of domestic and wild mammals
	Monkeypox could not have aroused enough vigilance due to its low virulence
	The viral transmissibility or virulence can be increased due to gene mutations
	Bioterrorism attacks can accelerate the virus spread
	Some countries cannot eliminate monkeypox promptly

Multiple factors aid the world in eliminating the Outbreak/2022 (Table 1). The control measures should have been strengthened substantially worldwide after the WHO declared the outbreak a PHEIC. Unlike human immunodeficiency virus (HIV) infections, most MPXV infections in humans are likely self-restricted.[2-4,16] Unlike various infectious diseases (e.g., viral hepatitis, viral encephalitis, and coronavirus infection), identification of suspected MPX infection is relatively easy because of its skin lesions and clinical epidemiology (i.e., most human cases occur in young MSM

in the Outbreak/2022), although confirmation of MPX cases relies on laboratory detection. Unlike RNA viruses, MPXV is a DNA virus and mutates relatively slowly, hence MPX vaccines need not frequent updates. MPX spreads more slowly than COVID-19 and currently mainly circulates in MSM, although some children and women have been infected through close direct or indirect contact.[2-4] Moreover, MPX vaccines have been ready for mass production in some countries, because smallpox vaccines can be directly used for MPX, as suggested by various epidemiological studies and animal experiments,[6,9,10,31] which is also supported by the fact that MPXV and VACV are close to each other in phylogenetics.[6,22] In the Outbreak/2022, unvaccinated people in the USA had 14 times the risk of MPX compared to people who were vaccinated.[3] Unlike vaccination and infection of influenza and COVID-19, vaccination and infection of MPX probably lead to long-term robust immunity.[3,6,9,10,31] Collectively, it is easier for the world to eliminate the Outbreak/2022 outside Africa than to eliminate a large COVID-19 outbreak, and the global weekly new MPX cases have been rapidly declining (Figure 3).

On the other hand, multiple factors hinder the world from eliminating the Outbreak/2022 (Table 1).

First, MPXV has infected too many people in many countries in 2022 (Figure 1), and Figure 3 suggests that the Outbreak/2022 could not be eliminated in 2022.

Second, MPXV can infect various species of domestic and wild animals.[1-3,6,] Therefore, infected humans can spread MPXV to domestic or wild animals outside, which is supported by the fact that a domestic dog was infected with MPXV from an infected human in the Outbreak/2022.[32] Wild animals can be infected by contacting MPXV-contaminated rubbish of infected humans or by direct close contact with infected domestic animals or their meat, blood, body fluids, or possibly excrement**.** The Outbreak/2022 could thus lead to endemicity outside Africa.

Third, the widespread of MPXV in humans in 2022 facilitates the virus to generate adaptive mutations to increase its contagiousness in humans. If MPXV replicates more efficiently in the skin, the respiratory tracts, or mucous membranes of the eyes, noses, or mouths of humans, it could be more contagious and more virulent in humans simultaneously, as per the trade-off theory regarding the long-term evolution of virulence of pathogens.[33] This possibility is supported by the fact that smallpox, goatpox, and lumpy skin disease are all highly virulent and highly

contagious in their hosts.[34] Previous studies showed that clade I MPXV is more virulent and more contagious in humans than clade II MPXV.[6]

Fourth, the Outbreak/2022 could not have aroused the vigilance of many threatened human populations worldwide because of its low CFRs (approximately 0.049% as mentioned above) calculated above through the nonlinear regression. This could lead to multiple waves of human MPX infections in the coming years and realization of dangerous scenarios D, E, or F listed in Table 1.

Fifth, the Outbreak/2022 can provide live MPXV strains for laboratory engineering and bioterrorism attacks, which can accelerate the virus′ spread worldwide and change the future of the Outbreak/2022.[35] This is indicated by an international official exercise conducted in 2021 which showed that an engineered MPXV released by bioterrorists could cause 3.2 billion human infections and 270 million deaths.[36]

Sixth, some countries, particularly those in war or severe poverty, cannot eliminate human MPX infections promptly. They cannot identify and isolate human MPX cases promptly, and they have not stockpiled enough smallpox or MPX vaccines and antivirals. The global vaccine inequity and antiviral inequity that facilitated the spread of SARS-CoV-2 could be repeated with MPX.[27]

4 STRATEGIES TO ELIMINATE THE OUTBREAK/2022

As per the epidemiology and risks given above, the following strategies should be considered to eliminate the Outbreak/2022 outside Africa earlier (Figure 2B).

First, all countries should strengthen publicity and education regarding the risks, prevention, treatment, and control of the disease, favorably through new media which are more efficient in communication and more capable of avoiding stigmatization. All people should know how to report suspected human or animal cases of MPX to the government, public health agencies, hospitals, etc. Likely due to strengthened publicity and education, MSM in the USA are taking steps to protect themselves and their partners from MPX (48% of them reduced the number of sex partners, 50% reduced one-time sexual encounters, and 50% reduced sex with partners met on dating apps or at sex venues).[3]

Second, infected people should be isolated until they are no longer infectious, and their rubbish should be properly treated, to cut off the transmission of MPXV in humans and animals.

Third, MPX vaccines should be well stockpiled worldwide. The USA decided to stockpile 13 million doses of MPX vaccines in May 2022. Empirically, we think that the whole world can enhance stockpiled smallpox or MPX vaccines from the current 16 million to more than 100 million doses for emergent responses to the increased MPX risk. The stockpiled vaccines can be employed in endemic African countries if the Outbreak/2022 is eliminated in the near future.

Fourth, epidemiological investigation of humans and animals living in threatened areas should be strengthened in order to identify new human or animal cases promptly. As explained above, it is desirable to investigate whether cattle, goats, sheep, and pigs are susceptible to MPXV, which is important for the elimination of the Outbreak/2022 as they are populous and frequently in close contact with humans. It is also desirable to investigate whether MPXV infection could be latent or persistent in some primates and humans infected with HIV.

Fifth, if possible, family members, sexual partners, healthcare workers, and other close contacts of human MPX cases should be vaccinated imminently (ring vaccination) to block the transmission in affected regions. Favorably, if possible, all people unvaccinated against smallpox can be vaccinated voluntarily, which could enhance the vaccination coverage of MSM without stigmatization.

Sixth, the quarantine of imported animals should be strengthened. This is supported by the fact that pet rodents imported from Ghana spread the virus to pet prairie dogs in the USA in 2003, which further infected more than 70 people.[5]

Seventh, robust international collaboration in sharing epidemiological information and vaccines is needed to aid low- and middle-income countries to eliminate the Outbreak/2022.[37] Mass vaccination in Nigeria, the DRC, and other endemic African countries can not only protect people in these countries but also reduce the possibility of MPX spreading to other countries again.[38] Without this one health notion, large-scale outbreaks of MPX outside Africa will occur repeatedly.

Eighth, all countries should consider strictly restricting laboratory research with live MPXV to avoid laboratory spill-over events.[35]

5 CONCLUSIONS

Here we summarized the epidemiology of MPX through a literature review and elucidated the risks and the elimination strategies of this outbreak mainly based on the summarized epidemiology. We demonstrated that MPXV became more contagious and less virulent in 2022, which could result from the fact that the virus entered a special transmission network favoring close contacts and/or the possibility that the virus accumulated a few adaptive mutations. We gave the reasons to investigate whether cattle, goats, sheep, and pigs are susceptible to MPXV and whether infection of MPXV could be latent in some primates. We listed six potential scenarios about the future of the outbreak and multiple factors aiding or impeding the elimination of the outbreak. We showed that the control measures strengthened worldwide after the WHO declared the outbreak a PHEIC could well control but could not eliminate the outbreak in 2022. We listed eight strategies for the elimination of the Outbreak/2022. Collectively, this analysis provides novel insights into the risks and elimination of the Outbreak/2022.

AUTHOR CONTRIBUTIONS

J.M.C. conceived, designed, and supported this study, analyzed the data, and drafted the manuscript. R.H.Z. and J.W.C. made the core conclusion, analyzed the data, and revised the manuscript. R.X.C, H.Y.G, M.M.Z., S.M.H, Y.F.J, and G.H. L. collected and analyzed relevant data and revised the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data supporting the views of this analysis are available from the corresponding author on request.

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