Chapter

Monkeypox Disease Epidemiology and Virus Ecology: From Neglected to High Consequence Infectious Disease

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Abstract

This chapter examines the epidemiology and ecology of the monkeypox virus (MPXV), focusing on its emergence, transmission, geographical spread, reservoirs, and hosts, while highlighting its growing impact on global public health. MPXV was first isolated in 1958 in monkeys at a Danish laboratory. The first human case appeared in 1970 in the Democratic Republic of Congo (DRC), coinciding with smallpox eradication efforts. The WHO supported active surveillance of MPXV from 1981 to 1986. While the natural reservoir of MPXV is still unknown, it is likely tree squirrels and wild rodents. Transmission occurs through animal-to-human (primary) or human-to-human (secondary) contact, involving close contact or inhalation of respiratory droplets. Sexual transmission was also reported among men who had sex with men (MSM) during the 2022 outbreak. Historically, MPXV cases were mostly limited to Central and West Africa. In 2005, cases emerged in Sudan, and in 2003, the first cases outside Africa were reported in the USA. The 2022 epidemic, with significant human-to-human transmission, led the WHO to declare an international public health emergency in July 2022. Between 2022 and 2023, nearly 100,000 cases were confirmed in 117 countries, with a case-fatality rate under 0.1%, mainly affecting MSM.

Keywords: epidemiology, risk factors, mpox emergence, mpox outbreaks, mpox pandemic

1. Introduction

The monkeypox virus (MPXV), today classified as *Orthopoxvirus monkeypox*, or monkeypox virus [1], is responsible for the mpox disease (formerly monkeypox disease) [2].

MPXV was first isolated in a Danish laboratory in 1958 from smallpox-like skin lesions on monkeys from Singapore, hence the name "monkeypox." Prior to this discovery, in India in 1936, a major smallpox-like epizootic was described in Bengal rhesus monkeys and could hypothetically be associated with the mpox virus [3]. In addition, other mpox epizootics were also observed in some non-human primates

(*Cynomolgus spp.*, *orangutans*, *gorillas, Cercopithecus spp.*, *marmosets*, *Macaca philippinensis*, *Macaca mulatta*, and *Cercopithecus aethiops var. sabaeus*), whose biological secretions failed to reveal any type of poxvirus other than mpox virus [4]).

The first human case was identified in a nine-month-old infant in 1970 in Zaire, current Democratic Republic of Congo (DRC), in Equateur province [5].

As this case was reported during a period of intensified efforts to eradicate smallpox, the WHO supported an active mpox surveillance program in the DRC from 1981 to 1986 to assess the importance of this new nosological entity [6]. The results of this active surveillance led to the development of a model for predicting human-to-human transmission of mpox. According to this research, mpox had a very low probability of persisting in human populations in the absence of repeated animal contamination. The authors concluded that, at that time, mpox was not yet a major public health threat [6].

However, almost 45 years after the cessation of routine smallpox vaccination, which conferred cross-immunity against mpox, an increase in cases of this disease has been noted in several countries in Africa and outside of this continent in recent years, and this is beginning to constitute a serious public health problem [7]. In May 2022, an unusually high number of mpox cases with sustained chains of local transmission were reported from many countries where the disease is not endemic. This situation prompted the WHO to officially declare mpox a Public Health Emergency of International Concern (PHEIC) on July 23, 2022 [8].

2. Modes of transmission and risk factors

The mpox virus can be transmitted to animals and humans in two modes: (1) animal transmission or primary contamination and (2) human-to-human transmission or secondary contamination. Primary and secondary cases can be infected through

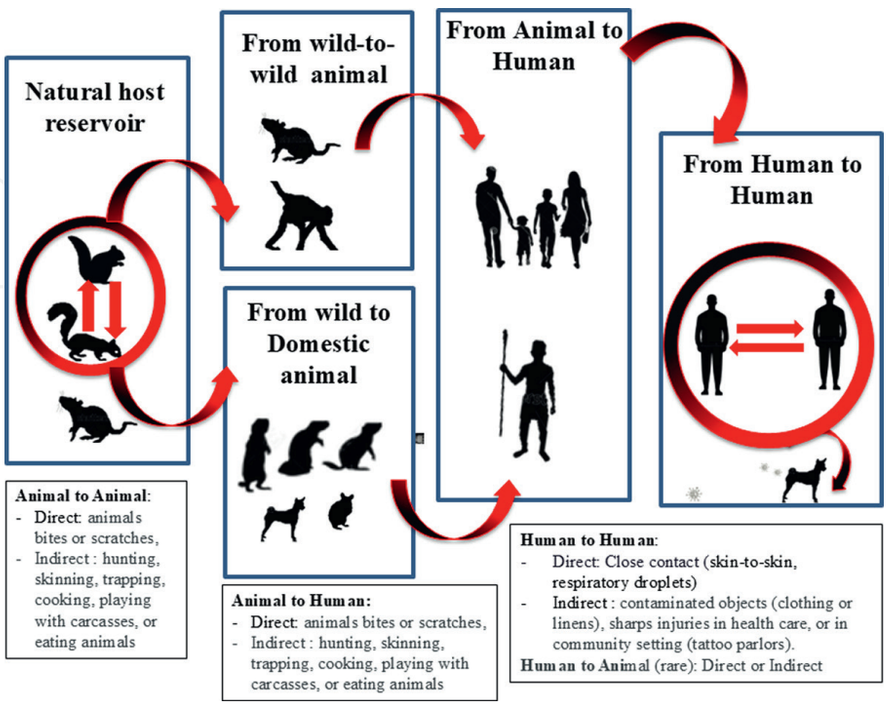


Figure 1.
Modes of MPXV transmission.

direct and close (skin-to-skin) contact with infected humans or animals or through their bodily fluids or fomites (**Figure 1**) [6, 9]. Human-to-human transmission can occur either through inhalation of respiratory droplets or close contact with the body secretions of an infected person or fomites [10] or through vertical transmission during pregnancy (congenital simian orthopoxvirose) [11]. During the 2022 epidemic, the mpox virus circulated mainly among men who have sex with men (MSM), probably through sexual contamination [11].

At the beginning of the mpox emergence, it was observed that animal or primary transmission was predominant and essential and was estimated at 78% in early studies [12]. Today, there is a clear trend toward a change in the mode of transmission of the disease, as the 2022 epidemic was characterized by very high human-to-human transmission, greater than 95% [11].

People living in villages close to dense forests seem to be at greater risk. Subjects at risk are mainly young boys not vaccinated against smallpox in endemic areas, due to the increased susceptibility of this population to the disease. However, the 2022 epidemic showed a higher proportion of older patients who had not been vaccinated against smallpox [13].

3. Geographic expansion in Africa

Since the notification of the first human case in the DRC and prior to the 2022 pandemic, the majority of mpox cases were confined to tropical rainforest areas of the Congo Basin and West Africa [14]. However, in 2005, the geographical distribution of the disease appeared to change, with cases occurring outside the preferred forest zones of Central and West Africa and specifically in Sudan (**Figures 2** and **3**) [15].

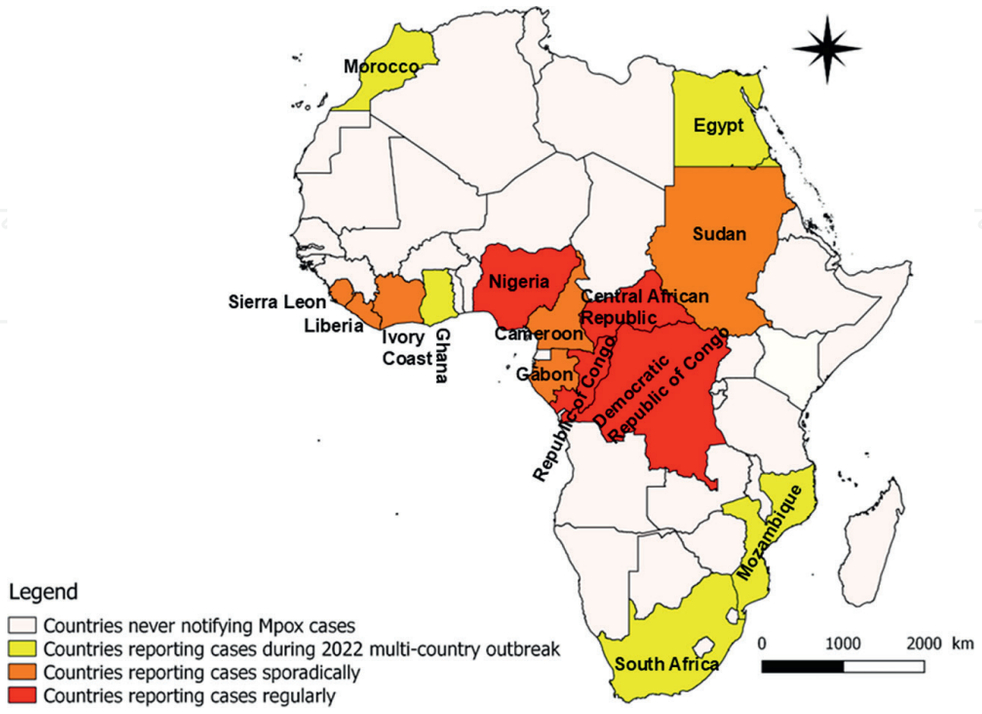


Figure 2.
Countries reporting human monkeypox cases in Africa from 1970 to 2024. For the elaboration of this figure, this work used published sources (research articles, reviews, and WHO reports).

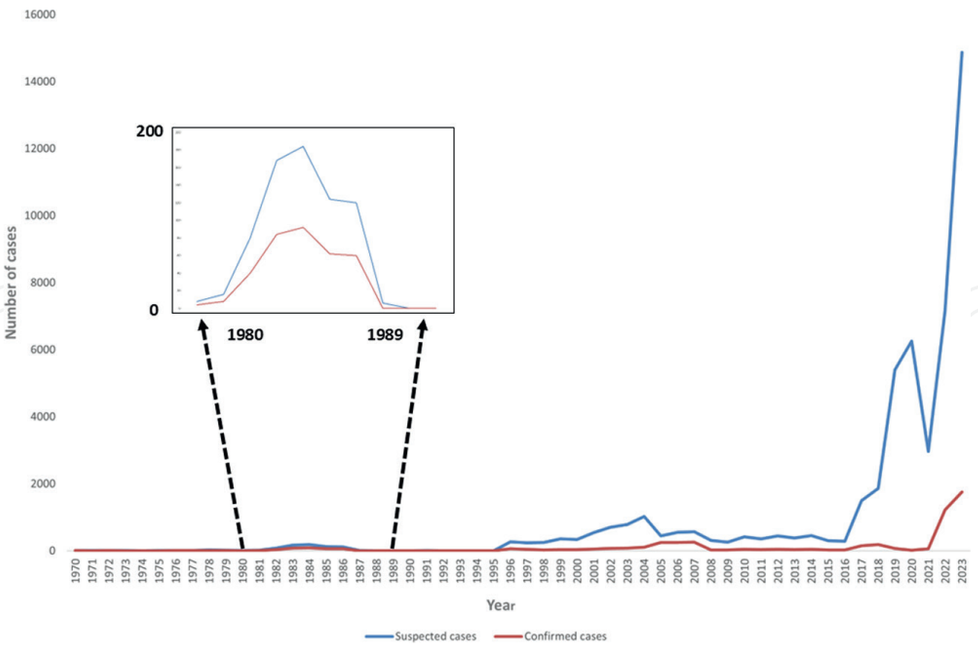


Figure 3.
Timeline of suspected versus confirmed monkeypox cases in Africa, 1970–2023. For the elaboration of this figure, this work used our world in data on https://ourworldindata.org/mpox.

3.1 Mpox of west and Central Africa

In West Africa, human mpox occurred in four countries, namely Nigeria, Ivory Coast, Liberia, and Sierra Leone [14]. Mpox cases appeared in five countries of Central Africa: Cameroon, the Central African Republic, DRC, Gabon, and the Republic of Congo [16, 17].

Between 1970 and 1979, 47 mpox cases were reported in Africa, including 38 in the DRC. Eight patients died, representing a case-fatality rate of 17%. Of these, 83% of patients with clinical signs were children under 10 years of age. Secondary human-to-human transmission was observed in only four cases, representing a secondary attack rate of 7.5% [18].

Between 1970 and 1986, 404 new cases of mpox were reported through the WHO's active mpox surveillance program (1981–1986). Of these, 386 cases of 404 were reported from the DRC, of which 338 cases came from regions where intensive epidemiological surveillance had been set up. Two hundred and forty-five of these three hundred and thirty-eight cases were associated with animal-to-human (zoonotic) contamination, giving a primary transmission rate of 72%. Children were the most affected age group (86% aged under 10, with an average age of 4.4). Deaths occurred in one in ten cases, well below the 17% observed prior to 1980 [6].

From 1986 (the end of the WHO's intensive surveillance program) to 1992, 13 cases of mpox were recorded in Central Africa, namely in Gabon, Cameroon, and the DRC. Between 1993 and 1995, no cases were reported, probably due to a poor mpox surveillance system during this period. Between 1987 and 1995, thirteen cases were documented, including six in 1987, one in 1990, five in 1991, and one in 1992. Of these thirteen patients, one was reported in Cameroon, ten in Gabon, and two in the DRC. These cases involved children only. It was also found that no cases were notified between 1993 and 1995 [19].

Between February 1996 and October 1997, the DRC recorded its largest-ever mpox epidemic. The epidemic was reported in the Katako-Kombe and Lodja health zones (Sankuru health district, Kasai Oriental province, DRC). A total of 511 suspected cases were identified, with mortality ranging from 1.5–3%. Men were most affected (58%), and the epidemic mainly concerned children under 16. This epidemic was marked by substantial human-to-human transmission, estimated at 78% of cases. Nevertheless, the low proportion of cases confirmed biologically and the low case-fatality rate observed suggested that a good number of cases could be attributed to varicella, the clinical features resembling that of mpox [20].

Between January 1998 and December 2002, the DRC reported 31 mpox patients [21], while the Central African Republic reported four cases in 2001 [22]. During the same period, a total of 1265 suspected cases of MPX were reported by the DRC Ministry of Public Health, of which 565 (44.6%) were aged between 10 and 24 years [23]. Only 41% of these cases were biologically confirmed among the 215 samples tested. From January 1, 2001, to December 31, 2004, the DRC's passive disease surveillance system recorded 2734 suspected cases of mpox. Of these cases, 380 were notified in 2001, 545 in 2002, 783 in 2003, and 1026 in 2004 [24].

From November 2005 to November 2007, a total of 760 biologically confirmed cases of mpox were reported in nine health zones of the Sankuru district through the active mpox surveillance project piloted by the University of Kinshasa School of Public Health, the University of North Carolina, and the US Army. Affected subjects had an average age of 11.9 years, and the majority (92.1%) were born after 1980, the period corresponding to the cessation of smallpox vaccination, which conferred cross-immunity against mpox [7].

In 2010, the Republic of Congo reported 8 suspected cases and 2 confirmed cases in the Likouala department [25], while the Central African Republic reported two confirmed cases [26]. From 2010 to 2014, passive surveillance by the Ministry of Public Health revealed that more than 2000 suspected cases of mpox were recorded each year, mainly in the Equateur and Kasaï Oriental provinces [27].

In 2014, 40 years after the last outbreak, an mpox epidemic occurred in Sierra Leone. During this outbreak, only one case was biologically confirmed [28]. Between December 2015 and February 2016, the Central African Republic reported 12 cases of mpox in the Bangassou and Mbomou provinces [29]. In August 2016, the Central African Republic also reported 26 suspected cases of mpox, including 3 confirmed cases in the provinces of Basse-Kotto and Haute-Kotto in Ref. [30]. Between September 2014 and February 2016, data from the DRC Ministry of Public Health notified 587 suspected cases of mpox [31].

From January to August 2017, an epidemic of 88 suspected cases of mpox, including 7 confirmed cases, had occurred in the Republic of Congo, and more specifically in the Likouala department [24]. In 2017, the Central African Republic recorded two epidemics. During the first outbreak, a total of 47 suspected cases (7 confirmed) were reported in February in Mbomou province [24], and during the second outbreak, a total of 3 cases (1 confirmed) were reported in April in Mbaki district [24]. During the same year, the Pujehan district in Sierra had reported a single isolated case of biologically confirmed mpox [24].

From September 2017 to August 2018, Nigeria recorded the largest mpox epidemic West Africa had ever seen. This epidemic occurred in 26 states, and 262 suspected cases, including 113 confirmed cases, were reported. Seven of the reported cases died, representing a case-fatality rate of 6.3%. The epidemic mainly

affected men (75%), the majority of whom were aged between 21 and 40, with a median age of 30 [32].

Between November and December 2017, Liberia had reported a total of 16 suspected cases, of which 2 were confirmed. This epidemic came 40 years after the last outbreak, which this country had experienced [24].

From the first to the 24th week of 2018, data from the Ministry of Public Health in the DRC had reported 2845 suspected cases of MPX [24]. In 2018, from March 17 to April 24, the Central African Republic reported 20 suspected cases of mpox, 9 of which were confirmed [24]. From March 30 to May 30, 2018, Cameroon had reported 16 suspected cases of MPX, including 1 confirmed [24].

In 2019, Cameroon recorded 1 confirmed mpox case in Ekondo Titi province, while the Central African Republic reported 18 suspected cases, of which 14 were confirmed in Lobaye and Ouaka provinces [33]. During the same period, a total of 5288 suspected cases of MPX were reported by the DRC Ministry of Public Health, of which 107 were deaths [33]. In the same year, Nigeria notified a total of 98 suspected cases, of which 47 were confirmed in 11 provinces; the Republic of the Congo reported 2 confirmed mpox cases in Gambona province, and Sierra Leone recorded 1 confirmed mpox case in Kailahun province [33].

In 2020, Cameroon reported 2 confirmed mpox cases in Ayos and Doumé provinces, while the Central African Republic notified 2 suspected cases and 8 cases in Mbomou, Sangha, and Mbaéré provinces [33]. In the same period, passive surveillance by the DRC's Ministry of Public Health revealed that more than 6216 suspected cases of mpox were recorded [33]. During the same year, Nigeria reported a total of 35 suspected cases, of which 8 were confirmed in Delta, Lagos, Plateau, Ebonyi, and Rivers provinces [33].

In 2021, Cameroon notified 4 confirmed mpox cases in Ayos and Nkambé provinces. During the same year, the DRC's passive disease surveillance system recorded 2841 suspected cases of mpox. In the same year, Nigeria reported a total of 98 suspected cases, of which 34 were confirmed in 9 provinces, and Sierra Leone recorded 1 confirmed mpox case in Koinadugu province [33]. From November 2021 to January 2022, the Central African Republic reported 42 suspected cases of mpox, 14 of which were confirmed. This outbreak occurred in Bania, Mambéré Kadéi prefecture, and the secondary attack rate was 59.5% (25/42) [34].

3.2 Mpox outbreak in Sudan

In October 2005, it was the first time that mpox occurred outside its preferred zone in the forests of Central and West Africa. Indeed, between September and December 2005, an MPX epidemic had been reported in Sudan's Unity State (now South Sudan), which is characterized by a semi-arid sub-Sahelian environment. A total of nineteen confirmed or probable cases were reported in the villages of Nuria, Rubkona, Wang Kay, and Modin. Nearly half (52%) of the cases were women, and the majority (80%) were under 20 years of age, ranging from 8 months to 32 years. No deaths were recorded. Although the cause of this epidemic was initially attributed to a new virus derived from the Central African strain [15], Nakazawa et al. demonstrated that the virus responsible for this Sudanese epidemic was genetically close to that of the northern DRC, casting doubt on the hypothesis of a new strain of mpox virus. The probable cause of this epidemic would be either the importation of animals from this northern part of the DRC to southern Sudan and/or a displacement of mpox-infected populations, taking into account the socio-political instability experienced by the region at the time of the epidemic and up to then [35].

4. Mpox outside of Africa

Outside of Africa, historically, there have been a handful of MPXV outbreaks involving animals in Europe and the United States with an uncertain origin of the disease [3]. To add more, human cases of mpox exported outside of Africa have been rare. The first human cases of mpox observed outside Africa were in 2003 during the epidemic in the US due to infested rodents imported from Africa [36].

There is a current trend toward wider geographical distribution of mpox epidemics. In recent years, MPX has spread outside Africa, notably to North America, Europe, and Asia. This extension is linked to the large-scale circulation of MPXV-infected people and the transport of naturally infected animals. In addition, this unexpected extension of the disease outside MPX's preferred African forest areas may be the result of the increased mobility of people and trade within and outside the African continent (**Table 1**).

4.1 First escape: Out to the USA

In May 2003, cases of MPX were reported in the state of Wisconsin. The disease was introduced to the USA by a shipment of 800 diseased exotic rodents imported from Ghana, including giant Gambian rats, African dormice, and ground squirrels. These diseased rodents contaminated the local prairie dogs housed alongside them in

Important events	Country	Time frame	Suspected/ confirmed cases	References
Isolation and characterization of mpox virus	Denmark	1958	—	[3]
Identification of the first human case in country	DRC (former Zaire)	1970	1/1	[5]
Active surveillance program started	DRC (former Zaire)	1981–1986	386/386	[6]
First in country large outbreak	DRC (former Zaire)	1996–1997	511/–	[20]
First outbreak outside Africa	USA	2003	82/47	[37]
First in country outbreak outside the tropical rain forest of Central and West Africa	South Sudan (former Sudan's Unity State)	2005	37/19	[35]
Re-emergence 40 years after silent phase	Sierra Leone	2014	1/1	[28]
Largest outbreak in West Africa	Nigeria	2017–2018	262/113	[32]
First in country outbreak	UK	2018	4/4	[38]
First in country imported case	Israel	2018	1/1	[39]
First in country imported case	Singapore	2019	1/1	[40]
Multi-country outbreak	117 countries	05/2022 to date*	/92030	[41]
First imported case in Sweden	Stockholm	2024	1/1	**

**by December 2023; DRC, Democratic Republic of Congo; UK: United Kingdom; USA: United States of America; **Ref. [42].*

Table 1.
Important events observed during mpox outbreaks between 1959 and 2024.

sales outlets. These infected animals transmitted the disease to the people who bought them through bites, scratches, or contact with their purulent secretions. The epidemic began in Wisconsin and spread to Indiana, Illinois, Missouri, Kansas, and Ohio. A total of 71 cases were reported, of which almost 40% were biologically confirmed. Patients ranged in age from 3 to 43 years, and both sexes were equally affected. No deaths were reported (**Figure 4**) [37].

4.2 Unexpected expansion

4.2.1 MPX outbreak in the UK

Two confirmed cases of MPX were reported in September 2018 in the United Kingdom (UK) in the towns of Cornwall and Blackpool, respectively. The two patients, although from Abuja in Nigeria, where an epidemic of MPX had occurred since September 2017 until that date, did not come from the same chain of contamination. These were the first cases of MPX to be recorded in Europe. One of these patients had transmitted the disease to a healthcare professional. Among the 134 potential contacts of this healthcare worker, the disease had only been transmitted to 4 people. No deaths were reported [38].

4.2.2 A case of imported MPX in Israel

A confirmed case of MPX was reported in Jerusalem, Israel, in October 2018. This case had been imported from Rivers State in Nigeria by a 38-year-old Israeli resident, who had frequented this region in which MPX was actively circulating. This was the first time MPX had reached the Asian continent. The patient did not die, and no cases of secondary contamination were reported [39].

4.2.3 A case of imported MPX in Singapore

In May 2019, Singapore notified a confirmed imported case of MPX. The patient was a man of Nigerian origin who had visited Singapore. The patient did not die. There was no evidence of secondary infection among the patient's contacts [40].

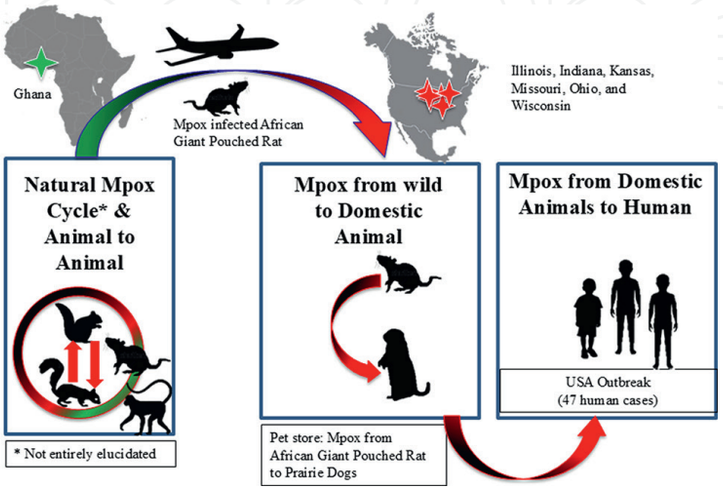


Figure 4.
Mpox out of America.

5. The twenty-first century mpox pandemic

The current mpox pandemic is believed to have originated from a source of MPXV Clade II from Nigeria, which occurred in May 2022 during the travel of an infected Nigerien resident to the United Kingdom. However, several introductions of viruses from Nigeria were also observed between 2017 and 2022 in the United Kingdom, Israel, Singapore, and the United States. Ultimately, one can consider that the actual pandemic which was the largest MPX epidemic in West Africa in history, due to the MPXV Clade II, spread in a pandemic manner, will have started in Nigeria in September 2017 [43]. Therefore, from the point of view of the circulation of MPXV in Africa, we can consider that Clade II actively circulates in West Africa in a human-to-human epidemic manner and that MPXV Clade I circulates independently in an endemic-enzootic manner in Central Africa [41].

5.1 A brief history of mpox emergence

Since it was first identified in laboratory monkeys kept for research in Denmark in 1958, the first human case of MPXV infection was recorded in DRC in 1970 and marked the recognition of mpox as a potential human disease. In the 1980s, human mpox cases were confined to remote areas of the rainforest regions of Central and West Africa. Furthermore, WHO reported for DRC two large outbreaks of hundreds of human cases in 1986 and in 1996; both events underscored the endemic nature of mpox in this region and its potential to spread more widely [15].

5.2 Re-emergence and global spread of mpox in the twenty-first century

In 2003, the first monkeypox outbreak outside of Africa was reported in the United States and spread among 6 states of the country with 71 human mpox cases. It was traced to pet prairie dogs that had been housed with imported infected African rodents from Gambia. This incident highlighted the risk of mpox global spread through the exotic pet trade [37].

After nearly 40 years without reported mpox human cases in the country, Nigeria experienced a significant monkeypox outbreak from 2017 to 2019 due to the MPXV West African Clade II, with over 146 confirmed and suspected cases [32].

Then, in 2021, mpox cases, linked to travelers from Nigeria, were reported in the United Kingdom, the United States, and Singapore [33]. These cases then indicated continued transmission in West Africa with, in fact, the beginnings of international spread. Indeed, a year after, a significant outbreak occurred globally. In early May 2022, an increasing number of human monkeypox (mpox) cases were reported in mpox non-endemic regions of multiple countries across Europe, the Americas, and Asia [44]. Ultimately, in the wave of COVID-19, the widespread nature of this outbreak led to increased public health measures and vaccination campaigns in affected areas. Since May 2022, when WHO declared the mpox outbreak a Public Health Emergency of International Concern (PHEIC), human mpox has emerged with nearly one hundred thousand cases confirmed from more than one hundred countries [13]. Indeed, by December 2023, there had been 92,030 confirmed cases reported in 117 countries.

While at-risk groups and the transmission dynamics of mpox mostly outside of Africa were due to the MPXV Clade II and revealed that more than 99% of reported

cases occurred among men having sex with men with a case-fatality rate (CFR) of <0.1%, the ongoing MPXV Clade I resurgence in several African countries showed only 2133 cases from January 2022 to December 2023, but with a higher case-fatality rate of 1.4 to 11%, mostly in young children (**Figures 5**–7) [45].

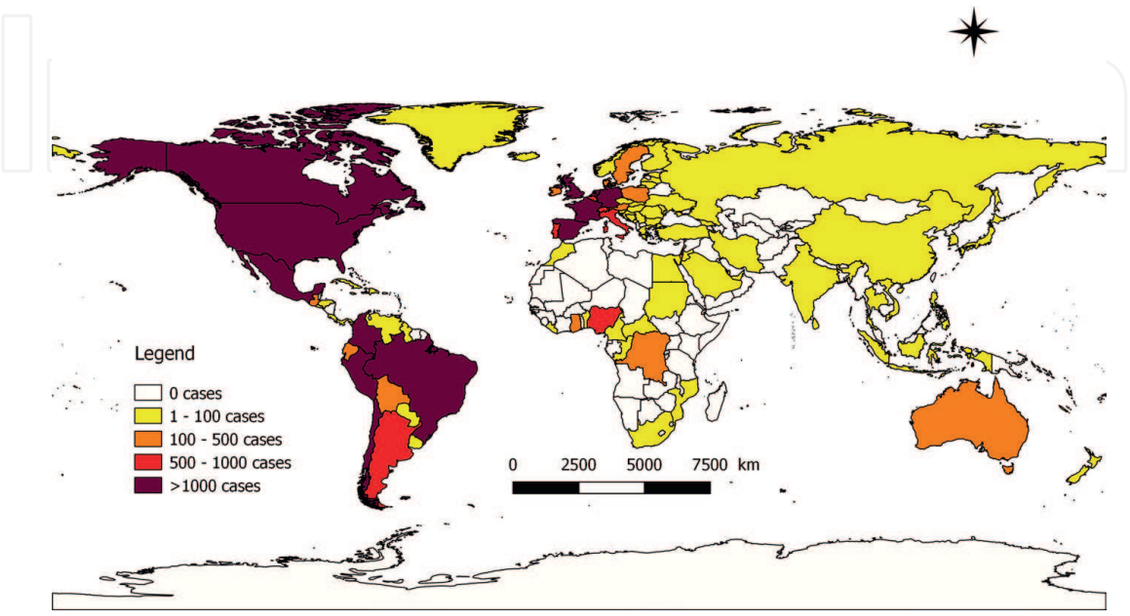


Figure 5.
Worldwide mpox situation during the pandemic from May to December 2022. For the elaboration of this figure, this work used our world in data on https://ourworldindata.org/mpox.

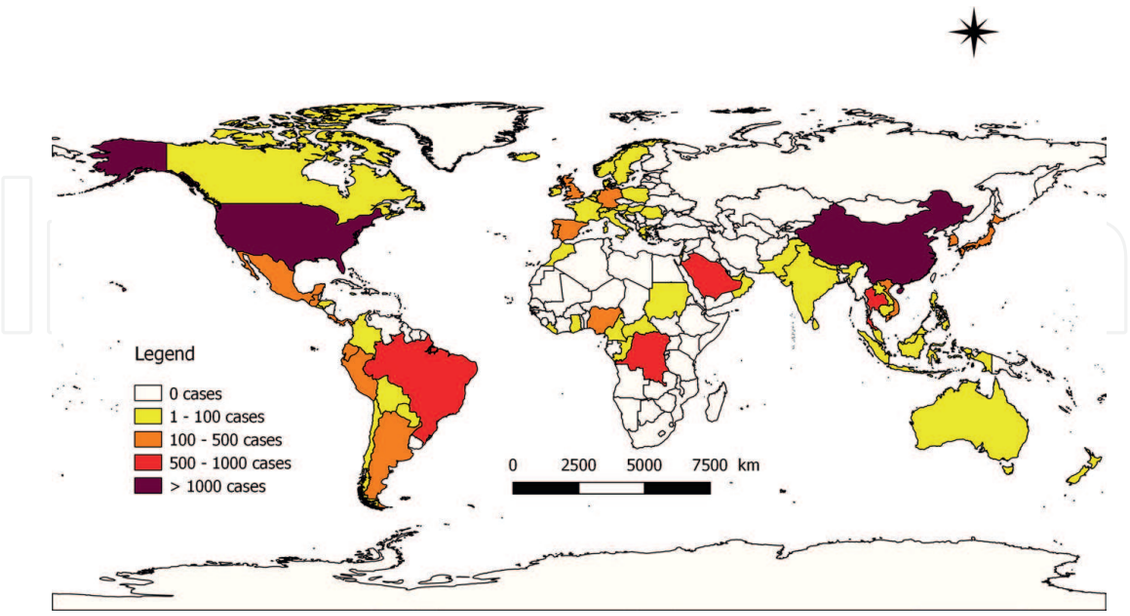


Figure 6.
Worldwide mpox situation during the pandemic from January to December 2023. For the elaboration of this figure, this work used our world in data on https://ourworldindata.org/mpox.

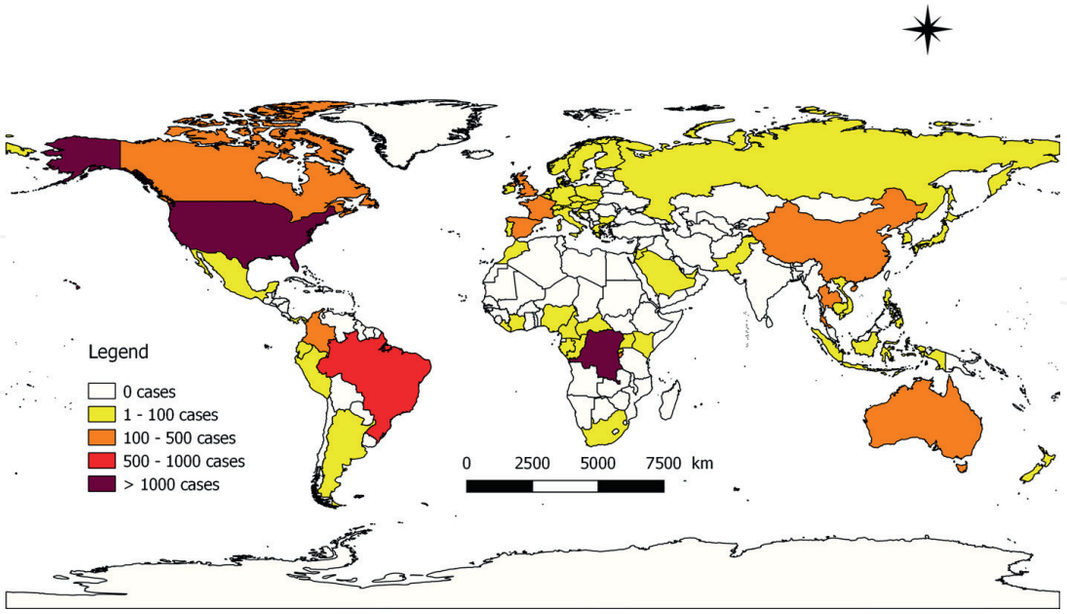


Figure 7.
Worldwide mpox situation during the pandemic from January to August 2024. For the elaboration of this figure, this work used our world in data on https://ourworldindata.org/mpox.

6. The monkeypox virus's natural history

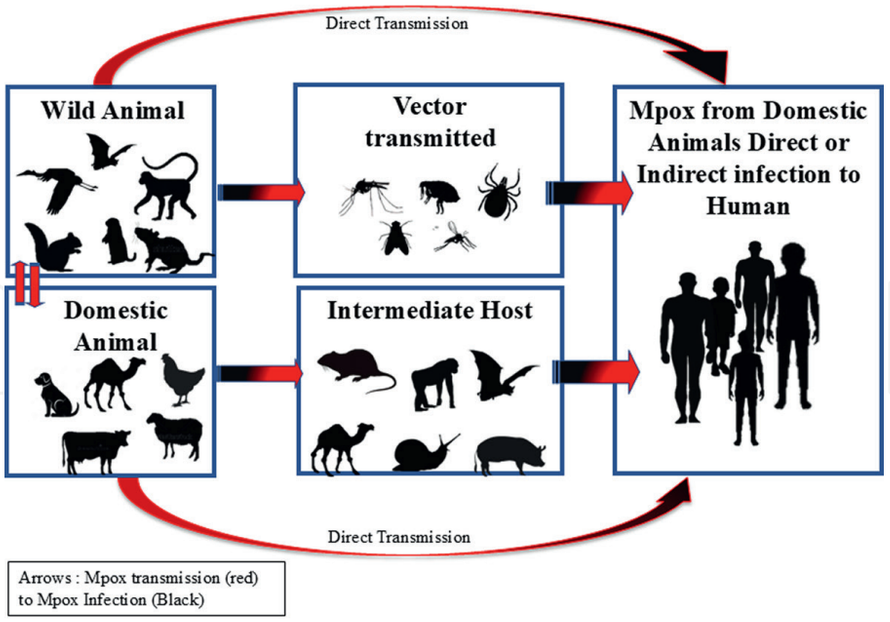
The MPXV comprises two distinct genomic groups, which are the West African Clade II and the Congo Basin clade I. These genomic groups have distinct and overlapping geographic distributions, with each having specific clinical and epizootological characteristics [46].

Today, the epidemiological pattern of mpox is changing with the global outbreaks, and the rising incidence of MPVX infections among young adults in the historical African endemic zones might be a result of the cessation several decades ago (1979) of the smallpox vaccine [47].

6.1 Virus natural reservoir(s) and hosts

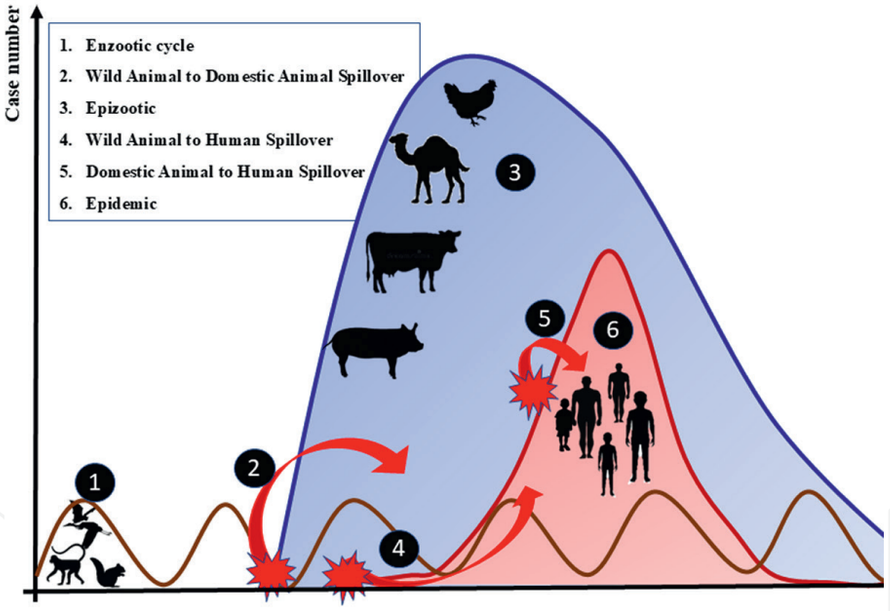
When the infection of humans and monkeys appears to be fortuitous, the natural wild animal reservoir of MPXV remains to be confirmed. Although notable progress has been made on the knowledge of hosts and reservoirs of the MPXV, several gray areas persist: Numerous serological surveys have shown that many animals can be infected in nature.

Until now, MPXV has only been isolated from the Thomas' rope squirrel (*Funisciurus anerythrus*) and the sooty mangabey (*Cercocebus atys)*; specimens from giant rats (*Cricetomys emini*) have also shown the presence of anti-Orthopoxvirus antibodies. In addition, several preliminary studies had consistently shown that certain monkey species from tropical Africa possessed anti-orthopoxvirus antibodies and/or MPXV-specific antibodies, such as the following species: cynomolgus monkeys (*Macaca fascicularis*); grivet *Cercopithecus aethiops*; lesser spot-nosed monkey (*Cercopithecus petaurista*); western red colobus (*Piliocolobus badius*), Mona monkey



Infectious diseases (ID) of Zoonotic Origine account for 60% of Human ID and 75% of Emerging ID

(a)



Source: Adapted from, William Karesh et al. 2012 Early detection and control efforts Lancet

(b)

Figure 8.
a. Zoonotic Disease Spread, the Actors. b. Zoonotic Disease Spread, the Mechanisms.

(*Cercopithecus mona*); Diana monkeys (*Cercopithecus diana*) [48, 49]. Rodents and other small mammals have also been suspected to be naturally infected, including the African dormice (*Graphiurus spp.)*; the tetradactyl horn rat (*Petrodromus tetradactylus*); chimpanzee (*Pan troglodytes*); red-legged squirrel, *Heliosciurus rubobrachium;* Congo rope squirrel (*Funisciurus congicus*) [50–52].

However, the primary reservoir of the MPXV remains unknown. From the original hypothesis of an exclusive simian reservoir (*Macaca fascicularis*) at the origin of the

discovery of MPXV [52], we have moved on to the hypothesis of a more diversified host-reservoir chain of transmission, through primates as secondary hosts of the MPXV transmitted from squirrels (*Funisciurus anerythrus*), from which the MPXV has so far been isolated in nature when several monkey species are known to prey on squirrels (**Figure 8a, b**) [28].

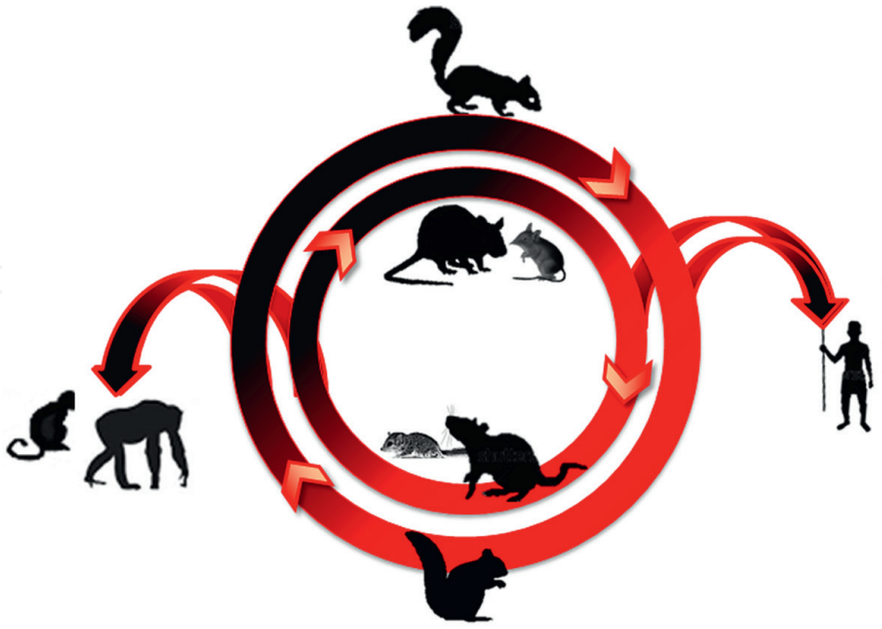
6.2 Understanding the natural cycles

The MPXV follows natural cycles that primarily involve interaction and zoonotic transmission between animal hosts and humans. We can thus distinguish two transmission cycles: a natural transmission cycle, which involves one or more natural animal hosts and accidental transmission (spillover) to humans; and an inter-human cycle, in which the virus becomes human and exercises its potential for intra-species transmission (**Figure 9**).

6.2.1 Natural cycle of transmission: The sylvatic cycle (forest cycle)

The sylvatic cycle is the natural cycle of monkeypox virus, which occurs mainly in the tropical forests of Central and West Africa. This cycle involves interactions between different animals, mainly rodents, which are the main natural known reservoirs of the virus (Rodents such as rope squirrels, Gambian squirrels, dormice, and African forest rats harbor the virus).

The natural reservoir hosts (primarily rodent squirrels) of MPXV are infected and develop viremia and skin lesions, which are still little documented in most suspected species. However, MPXV infecting animals suspected as a reservoir vector of the



Legend: The natural reservoir of Mpox and therefore the natural cycle of the virus remains unknown. However Squirrels of the genera *Funisciurus* and *Heliosciurus* as well as Rodents of the genera *Cricetomys, Graphiurus*, and *Petrodromus* appear to be related to the natural cycle. Also, frequently monkeypox virus has been identified from non-human primates' chimpanzees (*Pan troglodytes verus*) and monkey (sooty mangabey).

Figure 9.
Natural mpox cycle.

virus does not seem fatal, and horizontal intra- and inter-species transmission seems the most likely mechanism to hypothesize [53]. From the transmission point of view, the squirrel's potential reservoir of the virus has experimentally shown its capacity to develop viremia, infectious skin lesions, and possible inter-species transmission via respiratory droplets or other biologically infected products.

6.2.2 Domestic cycle of transmission: Human-human transmission

The domestic cycle occurs when the monkeypox virus passes from animal reservoirs to humans and then enters a human-to-human domestic cycle. This cycle involves several modes of transmission and can lead to human epidemics and the ongoing pandemic. Human-to-human transmission occurs by: (1) Direct Contact: Touching skin lesions, bodily fluids, or respiratory secretions of an infected person. (2) Contaminated Objects: Use objects contaminated by the bodily fluids of an infected person, such as clothing, sheets, or utensils [6, 9]. (3) Respiratory Droplets: Transmission by respiratory droplets emitted during coughing, sneezing, or talking [10]. Human index case contracts the virus through direct contact with bodily fluids, skin lesions, or respiratory secretions of infected animal or human. It can also occur from handling or consuming infected bushmeat.

Once a human is infected, the virus can spread from person to person through close contact with bodily fluids, skin lesions, or respiratory droplets from an infected person [6, 9].

Although it was less common than zoonotic transmission, as for today's pandemic, human-to-human transmission occurs much more frequently and is often facilitated by close, prolonged contact. Mpox can spread through close contact of any kind (kissing, touching, oral, and penetrative vaginal or anal sex) with someone who is infectious. Additionally, in September 2018, the virus was transmitted from a patient to a healthcare worker in the United Kingdom, probably through contact with contaminated bedding [38]. Also, international travel and human mobility can introduce MPXV to new non-endemic (i.e., not zoonotic) regions, where it can spread locally

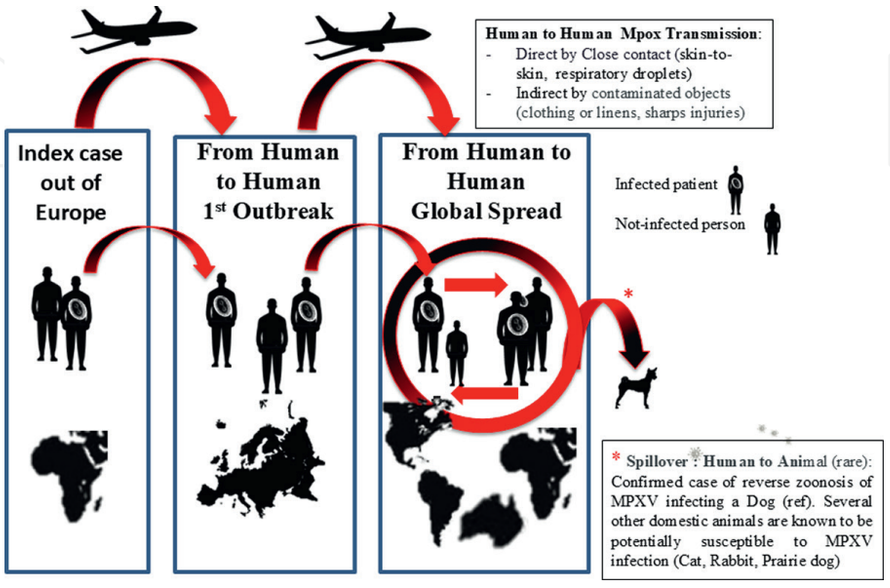


Figure 10.
Domestic human-to-human cycle.

if control measures are not put in place. In conclusion, the monkeypox virus mainly follows two cycles: the sylvatic cycle, which takes place among animal populations in tropical forests, and the domestic cycle, where the virus passes from animals to humans and can spread between humans. Understanding these cycles is essential for controlling and preventing monkeypox outbreaks, particularly in regions where MPXV is endemic (**Figure 10**).

7. Pandemic preparedness and readiness

7.1 Pandemic response

The areas of action for preparedness and response to the mpox pandemic include the priority areas of public health response, surveillance, community participation, and international support. The first response involves rapid diagnosis for the management of suspected or confirmed infected patients. Efforts to track and diagnose MPXV have improved over the years. Laboratory capacity to identify the virus has expanded, enabling quicker responses to outbreaks.

Immunization: The smallpox vaccine, which also provides protection against monkeypox, has been used in outbreak response efforts. The development and distribution of newer vaccines specifically targeting monkeypox are ongoing.

Education and Prevention: Public health campaigns have focused on educating communities about the risks of zoonotic transmission, the safe handling of animals, and the importance of vaccination.

Monkeypox remains a significant public health concern, particularly in regions where it is endemic. Increased global travel and trade have heightened the risk of international spread, making surveillance and preparedness critical. The history of monkeypox highlights the importance of understanding zoonotic diseases and their potential impact on global health.

7.2 Pandemic lessons: Forecasting the risk

Lessons from the pandemic. If the global mpox epidemic does not reach the scale of that of COVID-19, it also carries valuable lessons for preparation for future pandemics. Beyond the years of forgetting research on MPXV, then endemic for decades but only in Central Africa, the development of this mpox pandemic in the global north was a demonstrative element for the approach of global health, which today requires and is required to consider the risk of emergence due to zoonotic diseases on all continents with active surveillance.

7.2.1 Lessons learned and recommendation

The mpox pandemic revealed major shortcomings and thus provided some major lessons that must be followed, such as early detection of the index case and the area of emergence followed by a rapid response (contact tracing); reasoned confinement (isolation, quarantine) with communication (clear and coherent) and education of the general public (precise information on the disease, its transmission, and preventive measures); and the implementation of surveillance of populations at risk will be possible if there is targeted and dynamic health infrastructure and allocation of resources (supplies and training of health professionals).

7.2.2 Cooperation and partnership

The mpox situation showed how international cooperation could lead to an effective fight against the disease with an early exchange of data essential for diagnosis, the development of vaccines, and treatments. The rapid distribution of vaccines enabled local and then global control of the pandemic and demonstrated the importance of flexible multiple platforms for the rapid development of medical countermeasures.

What is more, for good management of epidemic risk, MPXV epidemics have essentially underlined the importance of equitable access to health services, vaccines, and treatments.

At national and international levels, coordination of rest was also essential and remains so; for example, the establishment of multi-sectoral coordination structures such as the National Institute of Public Health with Public Health Emergency Operation Centers.

Finally, and this was launched for the Ebola virus fever epidemic in 2014, a Pandemic Fund was launched by the World Bank.

7.2.3 The exercise of biosurveillance

Health surveillance, long neglected in endemic areas, often intertropical, and their populations at risk, today requires the implementation of a holistic approach within the well-defined framework of a One Health approach considering shared environments between humans (communities and individuals), hosts (domestic and wild), and potential reservoirs/vectors of the incriminated pathogen. This biomonitoring must also be carried out in the territories and at the borders with community participation and the detection (genomic and metagenomic) of potentially pathogenic agents. The mpox pandemic, like that of COVID-19, cruelly demonstrates the persistent global threat posed by the agents responsible for infectious diseases. By learning from these and past outbreaks, we can improve preparedness and response

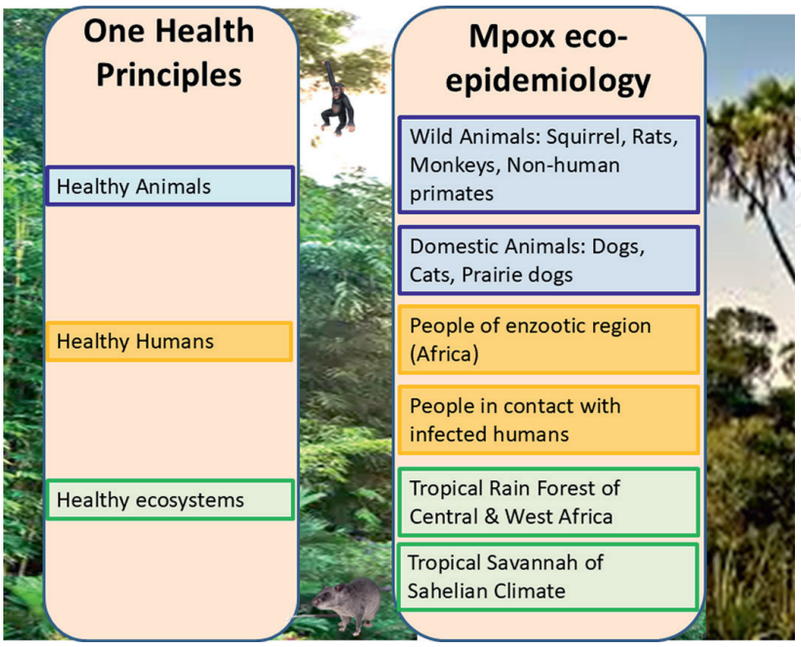


Figure 11.
One health and pandemic treaty.

strategies, eliminating the risk and/or mitigating the impact of future threatened outbreaks. After this double experience of the pandemics of the twenty-first century, enlightened actions are underway, such as the economic management of the risk and the proper resolution of the mpox epidemic [54, 55]. Accordingly, global risk awareness and the emerging Pandemic Treaty support the One Health approach that must be applied with veterinary and public health intervention teams trained specifically in zoonotic risk and multi-sectoral participation driven by environmental health (**Figure 11**) [56].

8. Conclusion

The risk of MPXV re-emergence remains a major concern, particularly in the context of global trade and increased interconnectedness of populations. Although previous epidemics were relatively contained, thanks to the pre-existing smallpox vaccine, the human-to-human transmission observed in 2022 showed that this virus, which has long remained endemic and epizootic in Africa, can now spread beyond its original borders. It is well known that zoonoses, such as MPXV, are closely linked to human interactions with wildlife and environmental changes, which increase the opportunities for viruses to pass between species. Thus, deforestation, rapid urbanization, and increased contact with animals carrying the virus amplify this risk. But human-to-human transmission exists and favors the rapid expansion of this virus in high-density populations. Thus, to prevent a new large-scale emergence, several measures must be put in place. First, it is crucial to strengthen epidemiological surveillance, particularly in endemic/enzootic regions and those that have already experienced epidemic outbreaks. Rigorous monitoring of human and animal cases, as well as early detection measures, would make it possible to rapidly contain any resurgence. However, the increasing mobility of humans is a factor in the spread of the virus that is difficult to control except during cross-border travel. Second, research into more effective vaccines and specific treatments must be intensified. While smallpox vaccines have shown some efficacy, better solutions adapted to this disease are needed. In parallel, increased awareness among the general public and health professionals is essential to recognize the symptoms and take appropriate measures, particularly when traveling to risk areas. Finally, it is essential to implement strategies to reduce contact between humans and wildlife through stricter environmental policies and responsible management of natural habitats. These combined actions can significantly reduce the likelihood of an uncontrolled re-emergence of monkeypox.

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