

Monkeypox: A New Challenge in Global Health Security

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Abstract Emerging viral zoonoses remain a global threat to public health with challenges to develop strategies for their control. Monkeypox, first identified in the Democratic Republic of the Congo in 1970, has become a growing global health concern, particularly due to its two distinct viral clades: the more severe Central African (Congo Basin) clade and the less virulent West African clade. Recent data from 2022 to July 2024 reports 37,583 cases and 1,451 deaths across 15 African Union Member States, with the majority occurring in the DRC. Nations of the world. Presently, the disease is found in more than 120 nations of the world, including India. Very recently, the World Health Organization declared monkeypox as a public health emergency of international concern. Clinical manifestations include fever, lymphadenopathy, headache, chills, rigor, and rashes on different parts of the body including the face, palm, soles and oral cavity. The disease can occur in sporadic as well as in epidemic form, and is more severe in children, pregnant women, and immunocompromised subjects. Laboratory assistance is required to make an unequivocal diagnosis of monkeypox. Most patients recover within 7 to 14 days. The resurgence of monkeypox, driven by several factors like increased global travel and reduced smallpox vaccination coverage, underscores the need for enhanced surveillance, public education, and preventive strategies, including vaccination and post-exposure prophylaxis, to control future outbreaks. The One Health approach seems imperative in the control of this emerging viral zoonosis that has posed a global public health threat.

Keywords: Central African clade, Emerging outbreaks, Monkeypox, public health, West African clade, Zoonotic diseases

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1. Introduction

Diverse zoonoses that are emerging or re-emerging can cause major illness and mortality in both humans and animals globally [1,2,3]. Monkeypox is an emerging and re-emerging zoonosis that causes sporadic human infections in Central and West Africa's forested areas [4]. Monkeypox (MPX) recently captured global attention, sparking concerns about a potential pandemic [5]. Although the disease is endemic to Central and West Africa, its true prevalence remains unclear. The first recorded case emerged in the Democratic Republic of the Congo in 1970 [6]. Phylogenetic analysis reveals two distinct clades of the monkeypox virus, each with unique geographic, epidemiologic, and clinical characteristics: the Central African (Congo Basin) clade and the West African clade. The Congo Basin clade, endemic in the Democratic Republic of the Congo, is notably more transmissible, leads to more severe illness, and has a case fatality rate (CFR) of up to 11%, with documented human-to-human transmission. In contrast, the West African clade exhibits a much lower CFR of less than 1% and no recorded

instances of human-to-human transmission [7].

The West African clade of the monkeypox virus has been isolated from outbreaks in Liberia, Nigeria, Sierra Leone, Ivory Coast, and the United States (primarily through imports from Ghana). In contrast, the Central African clade isolates originate from the Central African Republic, Cameroon, Gabon, Sudan, and the Democratic Republic of Congo [8]. The Congo Basin clade is more prevalent, particularly in the Democratic Republic of Congo, where it is endemic and over 2,000 cases are reported annually [9]. Between 1970 and 2018, a significant number of confirmed monkeypox cases were reported from equatorial Central and West African countries, including Cameroon, the Democratic Republic of Congo, Liberia, Ivory Coast, Ghana, Nigeria, and Sierra Leone, with mortality rates reaching up to 10% [10]. However, these figures likely underestimate the true burden of the disease due to limited testing and surveillance in African health systems. In Africa, monkeypox is often misdiagnosed, particularly with other rash-related illnesses; for example, 50% of suspected monkeypox cases in the Democratic Republic of Congo were misdiagnosed as chickenpox, which is caused by the Varicella-zoster virus [11]. The present communication is

an attempt to delineate the global public health emergency due to monkeypox virus.

2. Monkeypox Virus

2.1. Etiology

The monkeypox virus is a member of the *Orthopoxvirus* genus, which includes other double-stranded DNA viruses like cowpox (CPX), variola virus (VARV), and Vaccinia virus (VACV) [12]. It is distinguished by its oval or brick-shaped structure, measuring 200–400 nm, and is enveloped by a lipoprotein layer, visible under an electron microscope [13]. The genome of the monkeypox virus closely resembles other viruses within the *Orthopoxvirus* genus, featuring a 6,379-bp terminal inverted repeat, which contains a putative telomere resolution sequence and short tandem repeats [14].

The monkeypox virus can enter a host cell through two primary mechanisms. The first involves the fusion of viral envelope ligands with host cell plasma membrane receptors, such as chondroitin sulfate or heparan sulfate, leading to the dispersion of parts of the viral envelope into the plasma membrane. The second mechanism is endosomal uptake via macropinocytosis, which relies on actin [12]. Once inside the cell cytoplasm, the virus releases viral proteins and enzymes that disrupt cellular defenses and promote the expression of early genes, resulting in the synthesis of early proteins, DNA replication, and the production of intermediate transcription factors. It's important to note that monkeypox should not be confused with benign epidermal monkeypox (BEMP), a poxviral disease in primates caused by the *Tanapox* virus, which belongs to the genus

Yatapoxvirus in the *Poxviridae* family and is antigenically unrelated to the monkeypox virus [12].

2.2. Epidemiology

Monkeypox is endemic to the tropical rainforest regions of Central and West African countries, including Cameroon, the Central African Republic, Côte d'Ivoire, the Democratic Republic of the Congo (DRC), Gabon, Liberia, Nigeria, the Republic of the Congo, and Sierra Leone. Most cases occur sporadically or within localized outbreaks [13]. The virus is native to the rainforests of Central and West Africa [15].

The first human monkeypox infection reported outside of Africa occurred in 2003 in the United States, following a shipment of rodents imported from Ghana to Texas. This outbreak resulted in 81 cases, 41% of which were laboratory-confirmed [16]. In the same year, 11 cases and 1 death were reported in the Democratic Republic of the Congo, while in 2005, Sudan reported 10 cases. More recently, between September and December 2017, Nigeria reported 89 confirmed cases and 228 suspected cases of monkeypox across 24 of its 36 states [16]. Monkeypox cases are reported from many nations of the world [17]. The geographical distribution of recorded monkeypox locations worldwide is shown in Figure 1.

In endemic countries, monkeypox transmission occurs year-round without a specific peak month or season. The incidence of infection is similar in males and females, with no racial predisposition. During epidemics in Africa, children under 15 years of age have been the most affected, likely due to the discontinuation of smallpox vaccination [18]. Several cases of monkeypox with unusual clinical presentation have been reported from India [19].

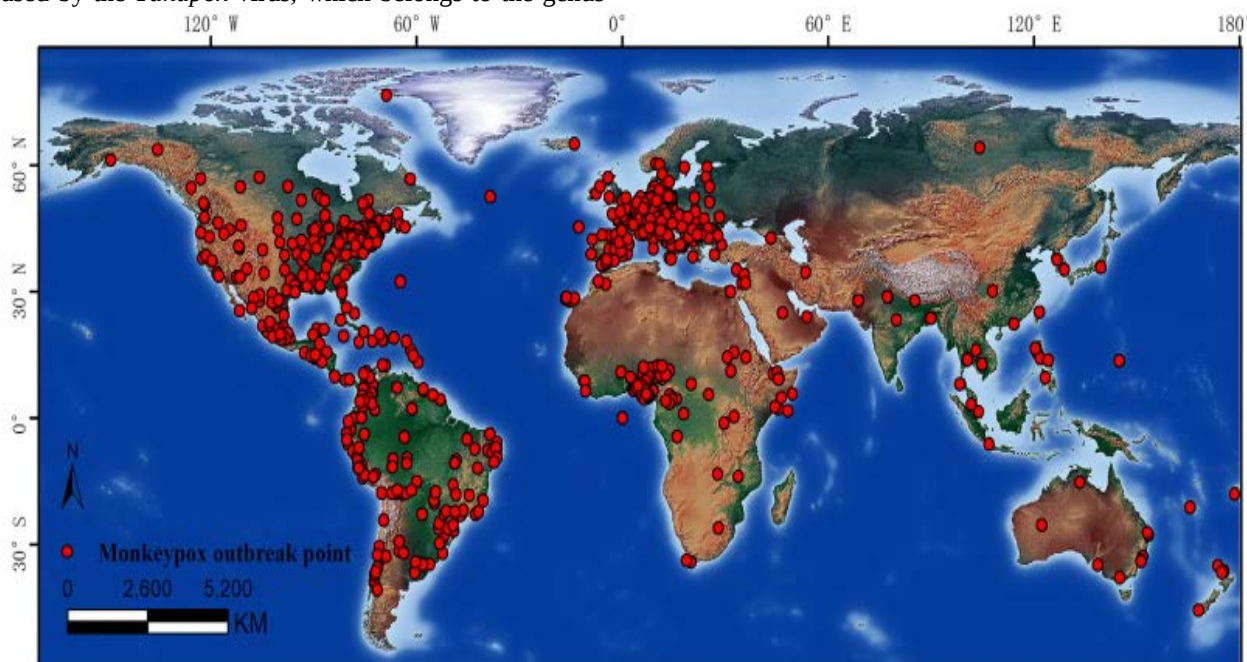


Figure 1. Geographical distribution of recorded monkeypox locations worldwide (Source: [17])

2.3. Transmission

Monkeypox is primarily transmitted through direct contact with infected animals or possibly by consuming their undercooked meat. Monkeypox primarily affects animals, but human-to-human transmission can occur through direct skin-to-skin contact with lesions (both skin and mucocutaneous) and bodily fluids such as pus, fluid, or blood from skin lesions [5]. It can also be transmitted via the placenta, resulting in congenital monkeypox, or through close contact during and after birth [20].

Infection can occur via cutaneous or mucosal lesions on animals, particularly when the skin barrier is compromised by bites, scratches, or trauma. The virus can also be transmitted from a range of animal reservoirs in Western Africa, including prairie dogs, rabbits, rats, mice, squirrels, dormice, monkeys, porcupines, and gazelles. Additionally, the infection can spread through respiratory contact with an infected animal or person [15].

In monkeypox outbreaks, direct physical interaction is the most common transmission method, especially in small communities where hunting and gathering occur. In the current multi-country outbreak, most cases have been reported among men who have sex with men (MSM), though evidence of sexual transmission is variable [20]. While no specific animal species has been definitively identified as the reservoir, rodents are often studied as potential carriers. Human-to-human transmission is also possible through large respiratory droplets, and the virus can potentially spread from mother to fetus through the placenta [15].

2.4. Pathogenesis

The incubation period for monkeypox, from exposure to symptom onset, is typically 6 to 13 days, though it can range from 5 to 21 days [20]. During this time, individuals are not contagious. The virus multiplies at the site of inoculation before entering the bloodstream [21]. Prodromal symptoms, such as fever and lymphadenopathy, occur one to two days before the onset of lesions and are correlated with a secondary viremia. Infected patients may be contagious at this time [22]. Lesions typically first appear in the oropharynx before spreading to the skin. Serum antibodies are usually detectable by the time skin lesions develop [23].

2.5. Clinical Manifestations

Human monkeypox symptoms are comparable to smallpox symptoms; however, they are typically more severe. Though it can go up to 21 days, the incubation phase usually lasts 7–14 days. Fever, headaches, and aches in the muscles are some of the early symptoms. Usually appearing 1–3 days after the fever starts, the rash first appears on the face and extremities before moving to other areas of the body [24,20]. A distinguishing factor between smallpox and monkeypox is the presence of lymphadenopathy, which is unique to monkeypox [25]. A study covering 12 confirmed cases of monkeypox in India revealed that 42% were males and 58 % were females. In most of the cases umbilicated, papulo-pustular, and crusted lesions were mainly present on the genital regions

of the affected persons. In addition, the oral erosion with pharyngitis and lymphadenitis were observed in some of the patients [19]. The rashes of monkeypox are observed on different parts of the body as shown in Fig.2. [26,27,28].

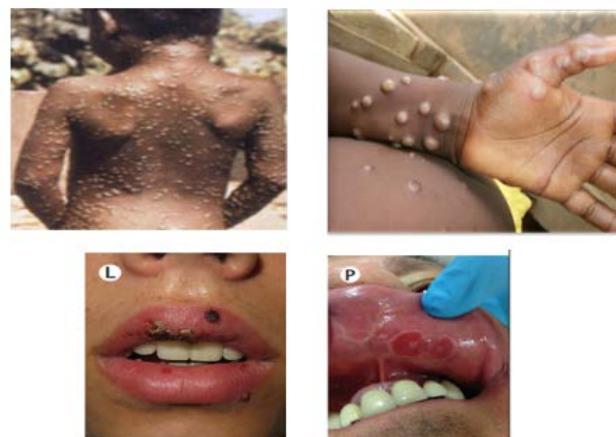


Figure 2. Clinical picture of monkeypox rashes on various parts of the body (Source: [26, 27, 28])

Several other rash illnesses can resemble monkeypox in clinical features, including chickenpox, smallpox, measles, syphilis, bacterial infections, and allergies. Lymphadenopathy is an early indicator that helps differentiate monkeypox from chickenpox or smallpox. However, recent outbreaks have shown a lack of prodromal symptoms. Therefore, if monkeypox is suspected, confirmation is achieved through a polymerase chain reaction (PCR) test, which is preferred for its accuracy and sensitivity [20,23,29,30].

2.6. Current Monkeypox Situation

Over 120 countries have reported mpox between January 2022 to August 2024, with more than 100,000 laboratory-confirmed cases reported and beyond 220 deaths among confirmed cases [26].

2.6.1. Monkeypox in Africa

From the beginning of 2022 through July 28, 2024, there have been 37,583 reported cases and 1,451 deaths (Case Fatality Rate [CFR]: 3.9%) across 15 African Union Member States: Benin, Burundi, Cameroon, Central African Republic (CAR), Congo, Democratic Republic of Congo (DRC), Egypt, Ghana, Liberia, Morocco, Mozambique, Nigeria, Rwanda, Sudan, and South Africa. In 2023 alone, 14,957 cases and 739 deaths (CFR: 4.9%) were reported from seven AU Member States, marking a 78.5% increase in new cases compared to 2022.

As of July 28, 2024, the year has seen 14,250 cases (2,745 confirmed and 11,505 suspected) and 456 deaths (CFR: 3.2%) from monkeypox across 10 African Union Member States: Burundi (8 cases; 0 deaths), Cameroon (35 cases; 2 deaths), CAR (213 cases; 0 deaths), Congo (146 cases; 1 death), DRC (13,791 cases; 450 deaths), Ghana (4 cases; 0 deaths), Liberia (5 cases; 0 deaths), Nigeria (24 cases; 0 deaths), Rwanda (2 cases; 0 deaths), and South Africa (22 cases; 3 deaths). This represents a 160% increase in cases and a 19% increase in deaths

compared to the same period in 2023. The DRC alone accounts for 96.3% of all cases and 97% of all deaths reported this year. Additionally, 24 suspected cases have been reported with no confirmed cases thus far [31].

Democratic Republic of Congo (DRC): As of July 30, 2024, DRC has reported a total of 13,791 monkeypox cases (2,628 confirmed and 11,163 suspected) and 450 deaths (Case Fatality Rate [CFR]: 3.3%) across 25 of its 26 provinces. This year, three new provinces have reported cases. Compared to the same period in 2023, there has been a 105% increase in cases and an 18% increase in deaths. Additionally, there was a 156% rise in suspected cases and a 36.5% increase in deaths in 2023 compared to 2022, indicating a persistent upward trend over the past three years. In 2024, 73% of reported cases have been male, and children under 15 years old account for 68% of cases and 85% of deaths. The clade I monkeypox strain has been isolated from confirmed cases, with the clade 1b variant identified in South Kivu Province in September 2023. Human-to-human transmission, including sexual contact, has been noted as a route of spread in DRC [31].

Burundi: As of July 28, 2024, Burundi has reported a total of eight confirmed monkeypox cases and no deaths. On July 25, 2024, the Ministry of Health reported three confirmed cases from the Bujumbura Nord, Gitega, and Isare districts. On July 22, 2024, three additional suspected cases were identified at Kamenge University Hospital, Kamenge Military Hospital, and Isare Health District. These cases presented with fever, joint pain, and a generalized rash. Blood samples from these cases tested positive for monkeypox via polymerase chain reaction (PCR) at the Burundi National Reference Laboratory. This marks the first outbreak of monkeypox reported in Burundi [31].

Central African Republic (CAR): Since the beginning of the year, CAR has reported 213 monkeypox cases (28 confirmed and 185 suspected) with no deaths, across 14 out of 35 districts [31].

Cameroon: In 2024, Cameroon has recorded 35 monkeypox cases (5 confirmed and 30 suspected) and two deaths (Case Fatality Rate [CFR]: 6.6%) from six of its ten regions: Adamawa, Centre, Littoral, Nord, Nord-Ouest, and Sud-Ouest. Of the confirmed cases, 80% were male. The clade II monkeypox strain was identified in the confirmed cases [31].

Congo: This year, Congo has reported a total of 146 monkeypox cases (19 confirmed and 127 suspected) and one death (CFR: 0.7%) across five of its twelve provinces. Among the confirmed cases, 56% were individuals over 15 years old, and 58% were male [31].

Ghana: As of the beginning of the year, Ghana has reported four confirmed cases of monkeypox with no deaths. Since the outbreak started in 2022, the total number of confirmed cases in Ghana has reached 131, with no deaths reported [31].

Liberia: In 2024, Liberia reported five confirmed cases of monkeypox with no deaths. The cases were distributed across two counties: Grand Kru (3 cases) and Nimba (2 cases) [31].

Nigeria: Since the start of the year, Nigeria has reported 24 confirmed cases of monkeypox with no deaths across 12 states and the Federal Capital Territory. Among

the confirmed cases, 50% were children under 10 years old, and 67% of those affected were male [31].

Rwanda: On July 25, 2024, the Ministry of Health reported two confirmed cases of monkeypox in the Gasabo and Rusizi districts. The first case is a 33-year-old female from Rusizi who exhibited fever and a skin rash at Islamic Health Center on July 20, 2024. The second case is a 34-year-old male from Gasabo who presented with a skin rash, fever, sore throat, and swollen lymph nodes at Kibagabaga Hospital on July 23, 2024. Both individuals had a history of travel to the Democratic Republic of Congo (DRC). Blood samples from both cases tested positive for monkeypox via PCR at the Rwanda National Reference Laboratory. This is the first reported monkeypox outbreak in Rwanda. Sequencing identified the monkeypox Clade Ia sublineage [31].

South Africa: On May 13, 2024, the National Department of Health declared a monkeypox outbreak in South Africa. To date, 22 confirmed cases and three deaths (Case Fatality Rate [CFR]: 14.0%) have been reported across three of the nine provinces: Gauteng (11 cases; 1 death), KwaZulu Natal (10 cases; 2 deaths), and Western Cape (1 case; 0 deaths). All reported cases are males aged between 17 and 43 years. One community death occurred in KwaZulu Natal. Sequencing results identified the monkeypox Clade IIb sublineage [31].

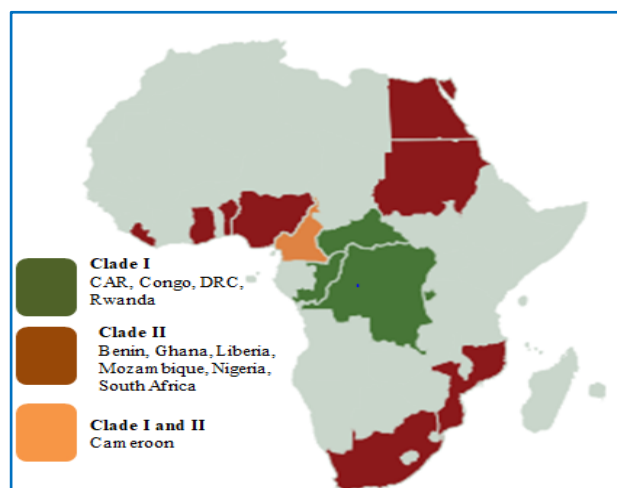


Figure 3. Map of Africa showing African Union Member States reporting monkeypox outbreaks, January-July 2024 (Source: [31])

2.7. Prevention and Control

Improved infection control measures are crucial in preventing monkeypox outbreaks among animals. This includes regular screening and isolation of newly infected animals to limit transmission. Enhanced hygiene practices are necessary to prevent the virus from spreading via contaminated fomites.

The smallpox vaccine has evolved through three generations of medical technology. Currently, only the second and third-generation vaccines are licensed for use. ACAM2000, a replication-competent smallpox vaccine, and IMVANEX (also known as JYNNEOS or IMVAMUNE; Bavarian Nordic, Hellerup, Denmark), a live, nonreplicating vaccine [32]. Both vaccines are applicable in two scenarios: pre-exposure for high-risk individuals to prevent infection and disease, and post-

exposure (ideally within 4 days) to improve outcomes if exposure occurs. [33].

The first-generation vaccines, such as Dryvax (Wyeth Laboratories, now part of Pfizer), used the live, unattenuated vaccinia virus and demonstrated a significant reduction in secondary attack rates (7.5% vs. 1.3%) among 2,278 household contacts in studies. However, subsequent first-generation vaccines were withdrawn because their production methods were crude to meet current licensure standards. ACAM2000, a second-generation, replication-competent vaccine, is derived from a single clonal viral isolate of Dryvax and has shown reduced neurovirulence in animal model studies [34]. However, it can lead to serious side effects, including progressive vaccinia, encephalitis, and eczema vaccinatum. It is contraindicated for immunocompromised individuals, those with skin disorders, individuals with underlying heart conditions, and pregnant individuals.

Replication-deficient modified vaccinia Ankara (MVA) is used in the third-generation vaccine known as IMVANEX. Strong humoral and cellular immune responses have been shown in investigations on non-human primates [35], and they offer clinical protection against severe monkeypox illness and mortality. However, clinical efficacy information for monkeypox in humans is still pending [36]. However, immunization campaigns in recently impacted nations have mostly targeted men who engage in sexual activity with men. Vaccines are primarily administered in North America and Europe, but are not yet available in African nations.

Comprehensive disease control plans were developed by national health authorities in endemic countries like Nigeria and the Democratic Republic of the Congo. These plans primarily included targeted epidemiological investigations in high-risk areas, improved laboratory-based surveillance capacity, laboratory diagnostics, the development of regional capacities to implement effective local responses, and heightened research activities [37]. However, these nations are unable to limit the spread of the disease or create a well-defined immunization plan due to a lack of access to the vaccine. If smallpox vaccination is not available, an alternative for post-exposure prophylaxis is vaccinia immune globulin [33,38].

Given that infections have been observed in Asian monkeys mixed with African primates, it is important to house these species separately. Individuals exposed to monkeypox should avoid contact with animals, especially rodents and non-human primates, to prevent further transmission [39]. During an epidemic, it is crucial to prevent the spread of MPX by isolating infected animals for at least six weeks from the date of exposure and monitoring their interactions. The areas where these animals were kept should be thoroughly cleaned and disinfected. It is important to adhere to the specific guidelines provided by healthcare authorities or the CDC website for proper management and prevention strategies.

To prevent infection with monkeypox virus (MPXV), follow these recommendations:

1. Avoid contact with animals that may be infected, including sick or dead animals in areas where monkeypox is known to occur.

2. Refrain from handling objects or surfaces that have been in contact with infected animals or humans.

3. Use personal protective equipment (PPE) such as gowns, masks, respirators, gloves, shoe covers, goggles, eye protection, and face shields when caring for infected individuals.

4. Implement isolation strategies for infected individuals to minimize the risk of disease transmission to others.

5. Practice proper hand hygiene by washing hands with soap or using hand sanitizer after interacting with sick humans or animals [39].

2.8. Re-emergence of Monkeypox Virus Disease

Several interrelated factors have contributed to the recent resurgence of infectious diseases. First, humans have encountered more frequent interactions with forest animals due to deforestation, armed conflicts, and migration. Second, the decline in herd immunity from the smallpox vaccination programs that ended in the 1970s has contributed to increased susceptibility. These two factors, though not mutually exclusive, represent the erosion of different protective barriers against disease spillover [40]. Increased global travel and commerce are exposing more people to potential infections. Strengthened economic, political, and cultural connections between humans facilitate both accidental and deliberate transmission of microbial agents. For instance, the United Kingdom, a non-endemic area, experienced three monkeypox outbreaks from May 25 to June 15, 2021 [41,42,43]. Studies suggest that human infections are unlikely to occur without repeated zoonotic spillovers. The growing interactions between humans and animals heighten the risk of diseases transferring from animals to humans [41,42,43].

Advancements in technology, including the increased use of invasive procedures like angiography and therapeutic medications for preventing thromboembolic events, have contributed to longer life expectancies. As the global population grows and life expectancy increases, there is a corresponding rise in vulnerable individuals. Factors such as the discontinuation of vaccination, a growing population, extended lifespans, and enhanced global connectivity due to easier transportation contribute to the potential resurgence of monkeypox [42].

2.9. Treatment

The use of antivirals that are active against the monkeypox virus is combined with general supportive care in the clinical management of monkeypox cases. Randomized or nonrandomized trials have not been carried out to assess the efficacy of any antiviral medication against monkeypox infection. Monkeypox may be treated with three antivirals: oral and intravenous tecovirimat [44,45,46], topical and intravenous cidofovir [47], and oral brincidofovir [48]. It is anticipated that these antivirals, which have been licensed for the treatment of smallpox based on safety data in healthy persons and animal models, will also be effective against monkeypox [48].

2.10. Conclusion and Recommendations

Monkeypox has emerged as a notable public health challenge, with a significant rise in cases both within its endemic regions in Central and West Africa and beyond. The two distinct clades of the virus present varying levels of severity, with the Central African clade posing a higher risk of severe illness and mortality. Despite its endemic status, the true prevalence and impact of monkeypox are likely underreported due to insufficient surveillance and diagnostic resources, particularly in affected African countries. Recent trends, including a sharp increase in cases and deaths, particularly in the Democratic Republic of the Congo (DRC), highlight the need for urgent and comprehensive public health responses.

Based on the above conclusions, the following recommendations were forwarded:

- Enhance surveillance systems and diagnostic capabilities in endemic regions to improve the detection and reporting of monkeypox cases.
- Develop and integrate advanced surveillance systems for early detection and rapid response to monkeypox outbreaks.
- Implement and enforce robust infection control measures in healthcare settings and communities to prevent the spread of monkeypox.
- Support research into monkeypox, including studies on vaccine efficacy and the development of new vaccines and treatments.
- Emphasis should be given to have multidisciplinary approach involving experts from veterinary, medical and environmental disciplines for control of emerging and re-emerging zoonoses including monkeypox.

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Contribution of Authors

All the authors contributed during the preparation of the manuscript.

Conflict of Interest

No conflict of interest was noticed among the authors.

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