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From Covid to Monkeypox: The Next Chapter in Viral Outbreaks

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Abstract Emerging and re-emerging viral zoonoses are important cause of morbidity and mortality in the developing and developed nations of the world. The re-emergence of monkeypox has garnered global public health attention. Originally identified in humans in 1970, monkeypox is categorized into two primary clades: Clade I (Congo Basin) and Clade II (West African). The recent global outbreak, mainly involving Clade IIb across 15 African Union Member States, revealed an expanded geographic distribution and shifting transmission patterns. Outbreaks of monkeypox also occurred in non-endemic countries. While monkeypox has traditionally been spread from animals to humans through infected wildlife, recent outbreaks show increased human-to-human transmission, with evidence suggesting reverse zoonosis to pets. This review consolidates current knowledge on the virus's etiology, host range, epidemiological trends and examines the clinical symptoms, diagnostic complications, ongoing efforts in treatment and prevention. Although smallpox vaccines and antiviral treatments like tecovirimat and brincidofovir exist, controlling monkeypox remains challenging due to evolving transmission routes and severity. Strengthening surveillance, vaccination strategies, and public health measures are essential to mitigating the impact of monkeypox and preventing future outbreaks.

Keywords: *Clade I (Congo Basin), Clade II (West African), Global outbreak, Orthopoxvirus, Monkeypox virus, Public health, Re-emerging viral zoonosis*

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1. Introduction

The re-emergence of various transmissible zoonotic infections, such as Zika, Nipah, Ebola, coronaviruses (including SARS-CoV-2), swine flu (H1N1), avian influenza (H5N1), and most recently, monkeypox [1]. Monkeypox, a zoonotic disease, affects various animals, including monkeys. Its abrupt re-emergence coincided with hopes that the 2019 coronavirus pandemic would decline, causing significant concern for public health and global economies [2].

Monkeypox is caused by the monkeypox virus, which belongs to the *Orthopoxvirus* genus within the *Poxviridae* family. The virus was first identified in 1958 when laboratory monkeys (*Macaca fascicularis*) in Copenhagen, Denmark, developed a pox-like illness after being transported from Singapore for polio vaccine research [3]. The first human case of monkeypox was reported in 1970 in an unvaccinated child in the Democratic Republic of the Congo (DRC) during efforts to eradicate smallpox. Since then, the virus has been classified into two main clades: the West African clade (Clade 2) and the Congo Basin or Central African clade (Clade 1). The Congo Basin clade is considered more virulent due to its higher mortality rate [4].

By May 2022, monkeypox cases had been reported in 109 countries, including those not traditionally considered endemic. In response, the World Health Organization (WHO) classified monkeypox as a moderate global public health emergency of international concern (PHEIC) on July 23, 2022 [5]. Numerous animal species can contract monkeypox, with the primary transmission route in endemic regions being contact with or consumption of infected animals. In humans, the virus is mainly spread through respiratory droplets and direct contact with lesions or scabs of an infected person; it can also be transmitted via contaminated objects (fomites). There have also been cases of congenital monkeypox, where the virus is transmitted from mother to fetus or infant [6]. The transmission of emerging and re-emerging diseases is intensified by factors such as increased deforestation, rising population density, extensive international travel, immigration, destruction of natural animal habitats, and inadequate epidemiological strategies for investigating

these diseases [7].

A recent report from France suggested a potential case of reverse zoonotic transmission of MPXV to a dog during the current MPX outbreak [8]; the animal tested positive for MPXV by cutaneous swab but negative by serology [9]. A single case of reverse transmission to a dog has also been reported in Brazil [10]. The reported cases of MPX in dogs suggest that there is the potential for reverse zoonosis transmission of MPXV (Clade IIb) [8,9,10].

Monkeypox can present with a range of severity, from moderate to severe and potentially fatal. It typically starts with a 1 to 4 days prodromal period characterized by fever, malaise, lethargy, and headache. This is followed by the development of well-defined macular, papular, vesicular, and pustular lesions that eventually crust over and shed. A key feature of monkeypox is the early onset of lymphadenopathy, which often occurs at the same time as the fever begins [11]. Common complications include pneumonitis, encephalitis, vision-threatening keratitis, and secondary bacterial infections. While most cases involve a cutaneous rash, it may be confined to areas such as the vaginal, perigenital, and perianal regions. Additionally, not all patients will experience prodromal symptoms like fever, malaise, and myalgia [12]. The present comprehensive review delineates the etiology, host range, epidemiology, pathogenesis, clinical spectrum, diagnosis, prevention and control of monkeypox that caused a challenge to national and international public health organizations.

2. Etiology

Monkeypox is caused by the monkeypox virus, a double-stranded DNA virus classified under the family *Poxviridae* and genus *Orthopoxvirus*. The virus was first isolated in 1958 during an investigation into a pox-like illness affecting monkeys and was later identified in humans in 1970 [11]. The virus's name is currently being reviewed by the International Committee on the Taxonomy of Viruses [13], and it is sometimes abbreviated as MPXV [14].

There are two distinct clades of the virus [13,15].

1. **Clade I**: Previously known as the Central African (Congo Basin) clade, it includes subclades Ia (formerly Clade I) and Ib. Clade Ib, a newly identified lineage, was first recognized in 2024 during an outbreak in the Democratic Republic of Congo (DRC), where sexual transmission was a significant factor [16]. A recent surge in Central and Eastern Africa is linked to clade I [17].
2. **Clade II**: Formerly called the West African clade, it includes subclades IIa and IIb. Clade II is associated with less severe disease, fewer fatalities, and reduced human-to-human transmission compared to Clade I [11]. The global outbreak caused in 2022 was due to clade II.
3. **Unknown Clade**: Countries like Liberia, Gabon and Guinea have reported cases of infection with an unknown clade and no mortalities [17].

The virus variants involved in the 2022 global outbreak belong to Clade IIb. This clade has been further categorized into lineages A.1, A.1.1, A.2, A.2.1, A.2.2, A.3, and B.1 [18,19,20]. The two clades of mpox exhibit notable distinctions in their pathogenicity and transmission dynamics. Clade I is associated with more severe disease outcomes and has a mortality rate of up to 10%, whereas clade II demonstrates a mortality rate of less than 4%. Transmission of clade I occurs primarily through rodent vectors, while clade IIb is currently spreading globally through human-to-human transmission [21].

3. Host Range

Experimental studies and field investigations have documented the monkeypox virus in various rodent species, including *Oryctolagus cuniculus* (rabbits), *Mus musculus* (mice), *Marmota monax* (woodchucks), hamsters, *Jaculus* sp. (jerboas), and *Atherurus africanus* (porcupines). Additionally, techniques such as molecular assays, virus isolation, and *in-vitro* contamination have been used to investigate the susceptibility of other animals, including black-tailed prairie dogs (*Cynomys ludovicianus*), anteaters, short-tailed opossums (*Monodelphis domestica*), giant anteaters (*Myrmecophaga tridactyla*), African hedgehogs (*Atelerix* sp.), southern opossums (*Didelphis marsupialis*), and various non-human primates [22,23]. The range of hosts and their susceptibility to monkeypox virus infection are further detailed in Table 1 [24].

In Africa, Asia, and Europe, various non-human primates, including chimpanzees (*Pan troglodytes*), orangutans (*Pongo pygmaeus*), cynomolgus monkeys (*Macaca fascicularis*), and sooty mangabeys (*Cercocebus atys*), can be infected with the monkeypox virus. In the USA and the UK, studies have shown that non-human primates [25,26,27] and common marmosets (*Callithrix jacchus*) are also susceptible to the virus, particularly when introduced via intravenous injection [28].

Non-human primates can exhibit signs and symptoms of monkeypox virus infection, whereas small mammals may carry the virus asymptomatically [29]. Serological investigations in African regions have detected the monkeypox virus in non-human primates, squirrels, and rodents, with wild animals showing a higher susceptibility to the disease. For example, in 1985, the monkeypox virus was isolated from Thomas's rope squirrel (*Funisciurus anerythrus*) in the Democratic Republic of the Congo, and in 2012, it was found in the sooty mangabey (*Cercocebus atys*) in Côte d'Ivoire. These findings suggest that such animal species may serve as reservoir hosts for the monkeypox virus [30].

Susceptibility to monkeypox virus infection was detected through investigational research in the laboratory. Transmission to humans has been previously documented in the literature [24].

Table 1. Host range and susceptibility of animals to monkeypox virus infection

Order/Family	Species	Tools of investigation	Relationship to human infections
Hominidae/ Primates	Homo sapiens (Humans)	Virus Isolation	Yes
	Pongo pygmaeus (Orangutans)	Virus Isolation	Yes
	Pan troglodytes (Chimpanzees)	Virus Isolation	No
Cercopithecidae/Primates	Cercocebus atys (Sooty mangabeys)	PCR/Virus isolation	No
	Macaca fascicularis (Cynomolgus monkeys)	Virus Isolation	Yes
Callithrichidae/Primates	Callithrix jacchus (White-tufted marmosets)	Laboratory infection	No
Chinchillidae/ Rodentia	Orycytolagus cuniculus (Rabbits)	Laboratory infection	No
Muridae/Rodentia	Mas musculus (Inbreed mouses)	Laboratory infection	No
Cricetidae/ Rodentia	Hamsters	Laboratory infection	No
Nesomyidae/Rodentia	Cricetomys species.(Giant-pouchedrats)	PCR/virus isolation	No
Gliridae/Rodentia	Graphiurus species..(African dormices)	PCR/virus isolation	No
Sciuridae/Rodentia	Funisciurus species.(Ropesquirrels)	PCR/virus isolation	Yes
	Cynomys ludovicianus (Black-tailedprairiedogs)	PCR	Yes
	Marmota monax (Woodchucks)	PCR/ virus isolation	No
Dipodidae/Rodentia	Jaculussp.(Jerboas)	PCR/ virus isolation	No
Hystricidae/Rodentia	Atherurus africanus (Porcupines)	PCR/virus isolation	No
Macroscelididae/Pilosa	Myrmecophaga tridactyla (Ant-eaters)	Virus isolation	No
Didelphidae/Didelphimorphia	Didelphis marsupialis (Southern opossums)	PCR/virus isolation	No
	Monodelphis domestica (Shot-tailed opossums)	PCR/virus isolation	No
Erinaceidae/Erinaceomorpha	Atelerix species .(African hedgehogs)	PCR/virus isolation	No

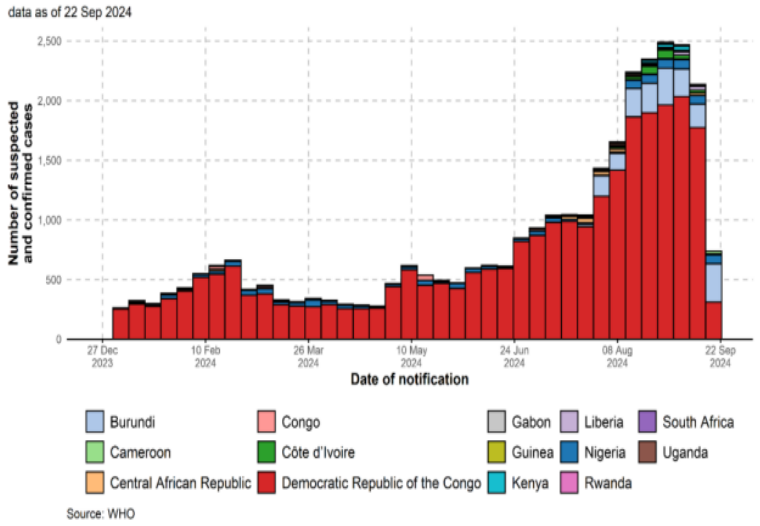

Figure 1. Epidemic Curve of confirmed mpox cases in Africa (As of 22nd September, 2024 *(32)*

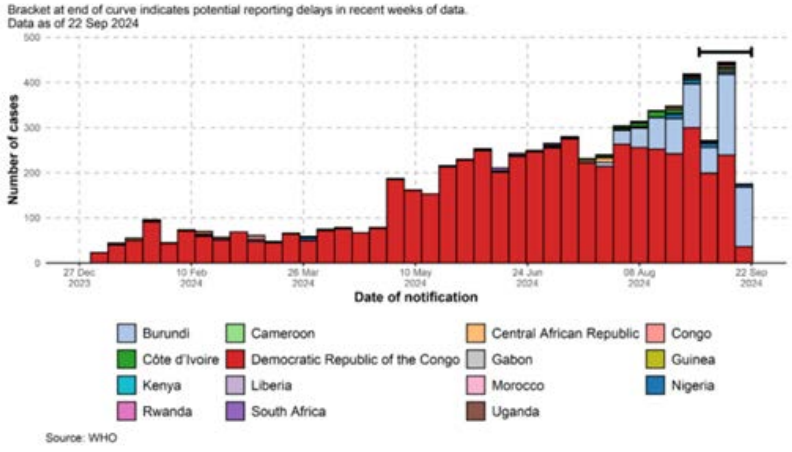

Figure 2. Epidemic curve of reported suspected mpox cases (tested and untested) in Africa, by reporting country, 1 January 2024 - 22 September 2024 *(32)*

4. Epidemiological Situation in Africa

As on 22nd September, 2024, 15 countries in Africa have reported 6603 confirmed mpox cases due to monkeypox virus clade I and clade II and over 844 suspected deaths (CFR 2.7%) [31, 32]. These countries are: Democratic Republic of Congo (DRC) (5621 cases), Burundi (696 cases), Central African Republic (CAR) (54 cases), Cote d'Ivoire (52), Nigeria (55 cases) [32] (Figure 1).

In 2023, a total of 14,838 confirmed and suspected monkeypox virus infections were reported from Cameroon, the Central African Republic (CAR), the Republic of the Congo, the Democratic Republic of the Congo (DRC), Ghana, Liberia, and Nigeria. Among these, the Democratic Republic of Congo reported the highest number of cases, with a cumulative total of 19,667 infections (including 2,961 confirmed and 16,706 suspected cases) and 575 deaths [31]. In the DRC, most cases and deaths occurred in individuals under 15 years old, representing 66% of the cases and 82% of the deaths. Additionally, 73% of all reported monkeypox cases in the DRC were among males [31] (Figure 2)

Burundi has most people with monkeypox due to clade Ib outside DRC and community transmission is presumed. According to the Africa CDC report of 25 August 2024, 190 confirmed and 512 suspected monkeypox and current monkeypox virus clade I outbreak a public health emergency of international concern [32] cases had been reported in total from Burundi in 2024 from 26 out of 49 health districts. On 13 August 2024, Africa CDC monkeypox a Public Health Emergency of Continental Security. On 14 August 2024, WHO a meeting of the IHR Emergency Committee to discuss the increase in people with [33].

5. Mode of Transmission

Monkeypox virus naturally infects certain rodents and primates in central Africa. Early human cases are usually associated with contact with infected animals, such as exposure to mucous membranes, body fluids, or tissues, or through the consumption of undercooked meat. Transmission can also occur from scratches or bites by infected animals [34]. Human-to-human transmission is thought to happen through direct contact with respiratory droplets from infected individuals [35,36,37] (Figure 3).

Additionally, the monkeypox virus can be transmitted vertically from infected mothers to their newborns [7,38]. This recent outbreak represents the largest monkeypox epidemic reported outside Africa, differing from previous outbreaks. Historically, monkeypox was diagnosed primarily through contact with infected animals or travel to regions affected by the virus [39,40,41]. In contrast, the current epidemic has shown that most cases are linked to sexual contact between individuals rather than exposure to infected animals or travel [18].

In the past two years, most reported monkeypox cases have been among homosexual or bisexual males. Research indicates that 98% of these cases were in this group, with 41% also co-infected with HIV. Furthermore, 73% of the lesions were located in the anal and genital areas [42,43]. The incubation period for monkeypox is approximately 7–14 days, with symptoms persisting for 14–21 days [44,45]. This extended incubation period can complicate diagnosis, potentially leading to delays in medical intervention, disease progression, and increased transmission risk [46,47].

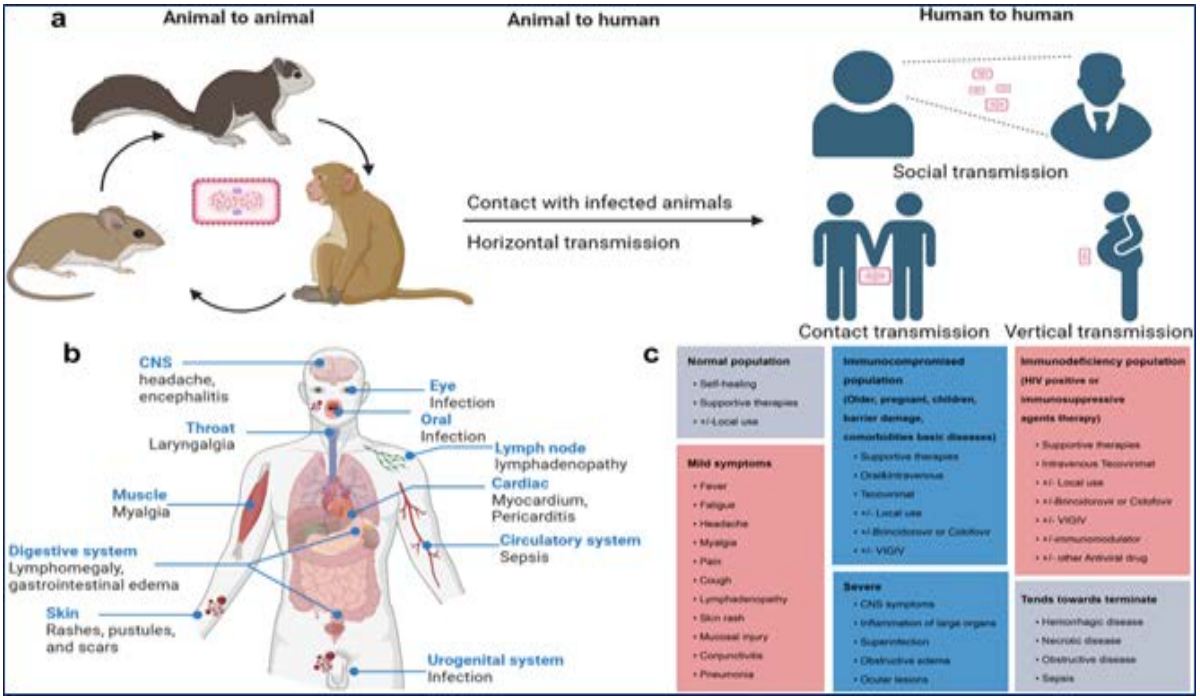

Figure 3. A. The transmission of Monkeypox occurs through animal-to-animal, animal-to-human, and human-to-human routes. B Clinical symptoms typically manifest after monkeypox infection. C Symptoms of Monkeypox infection may vary based on the immune status and clinical treatment options and clinical treatment options are listed

6. Risk Factors

The current monkeypox outbreak is linked to dynamics such as the increasing invasion of hominids into wild habitats, international and global public travel from enzootic regions to non-endemic areas, the introduction of pets and laboratory animals, a lack of active disease surveillance, and ineffective prevention and control strategies. Furthermore, the discontinuations of smallpox vaccine, as well as other instances of animals in captivity or experimental laboratories, have put the general people vulnerable to monkeypox virus infection or other *Orthopoxvirus* infections [48]. Nosocomial monkeypox virus infections are a serious risk factor for patients and healthcare workers in both enzootic and non-enzootic areas (nosocomial infections, also known as healthcare-associated infections (HAI), are infection(s) acquired during the process of healthcare service that were not present at the time of admission) [49]. The various risk factors associated with monkeypox cases are shown in Table 2.

Table 2. Risk factors associated with monkeypox cases

Risk factor	References
Age	In Nigeria, individuals affected by monkeypox were predominantly under 40 years old. This demographic increased susceptibility is linked to the absence of cross-protective immunity, as these individuals were born after the end of the smallpox eradication campaign (50).
Nosocomial infection	Healthcare-associated spread (51).
Zoonotic infection	Interactions with infected prairie dogs (52) and wildlife, bites from peri-domestic animals, and exposure to hunters (53) have been identified as transmission routes for monkeypox. Additionally, contact with household materials (54,55) and peridomestic rodents (56) can also facilitate the spread of the virus.
Travelers	Immigrants to non-endemic monkeypox regions (27).
Human to human transmission	Inter-human transmission (57).
Human-to-animal transmission	Human-to-dog transmission was reported in France and Brazil (8,58).
Men who have sex with men (MSM)	Monkeypox has been transmitted among men who have sex with men (MSM), including those engaged in bisexual contact and individuals with multiple sexual partners (59). The spread is particularly notable among young men who have sex with other men, especially those who practice unsafe sex and are HIV-positive. Additionally, retrospective records indicate a higher incidence of sexually transmitted diseases (STDs) such as syphilis among these individuals (60).

7. Pathogenesis

Monkeypox is generally a self-limiting disease, with its severity influenced by factors such as the viral strain, the individual's immune system, and any complications that may arise [61]. Early symptoms often include pain, fever, fatigue, and lymphadenopathy, with pronounced inguinal lymphadenopathy being a common feature [62]. This lymphadenopathy can help differentiate monkeypox from other *Orthopoxvirus* infections [63]. Effective management of monkeypox requires a clear understanding of its transmission routes. The virus typically enters the body through mucous membranes (such as those in the eyes, respiratory tract, mouth, urethra, or rectum) or broken skin following exposure to respiratory secretions or body fluids from infected individuals [64].

The monkeypox virus spreads through the body via tissue-resident immune cells and draining lymph nodes, a process occurring during the virus's latent period, which typically lasts up to two weeks [64,65]. During this period, infected individuals are usually asymptomatic and lack visible lesions. Following this latent phase, individuals start to show prodromal symptoms such as fever, chills, headache, muscle aches, and lymphadenopathy. These initial symptoms generally last for about three days. Subsequently, a rash develops, beginning on the face and head and then spreading across the body. This rash progresses from papules to vesicles, then to pustules, and finally forms crusts that heal and may leave scars. This rash phase typically lasts 2–4 weeks [66,67]. In the ongoing outbreak among men who have sex with men (MSM), some atypical clinical presentations have been noted, with rashes predominantly appearing in the genital or anal regions before spreading elsewhere [40,68].

8. Clinical Signs

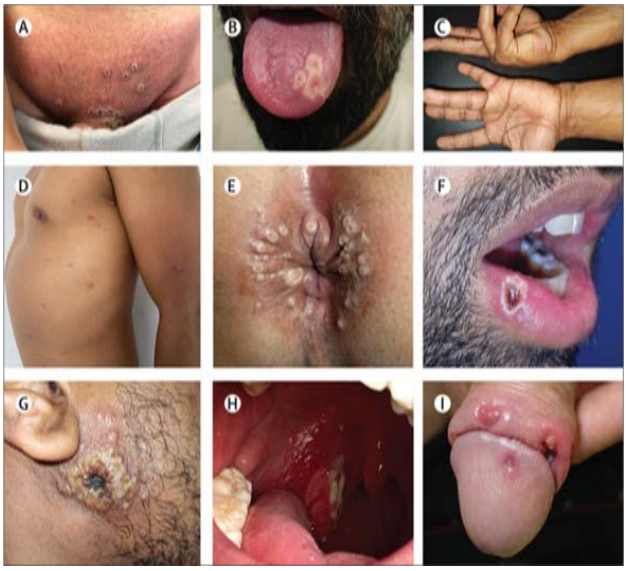

Figure 4. The clinical presentation and virological assessment of confirmed human monkeypox virus infections [73]

The monkeypox virus typically enters the host through several routes, including broken skin, respiratory tract openings, the eyes, the placenta, and occasionally the urogenital tract. Once inside, the virus replicates at the initial infection site before moving to nearby lymph nodes and spreading via the bloodstream, leading to viremia. This dissemination allows the virus to reach target organs and produce clinical symptoms (Figure 4). Mpox manifests with signs and symptoms that typically arise within one week of exposure, though the onset can occur anywhere from 1 to 21 days post-exposure. The duration of symptoms generally ranges from 2 to 4 weeks but may be prolonged in individuals with compromised immune systems [69]. Common symptoms include fever, headache,

muscle pain, and lymphadenopathy. As the infection progresses, lesions develop in the oral cavity, and full-thickness epidermal necrosis results in the crusting of rashes, especially on the face and limbs. It is important to note that infected individuals are contagious from the onset of fever until the veins have crusted. Other potential symptoms include pneumonia, visual impairments, and encephalitis. The current outbreak notably features a high incidence of lesions in the vaginal, perianal, and perioral regions [70]. A key distinguishing clinical feature of mpox is the presence of lymphadenopathy, which is absent in other conditions such as smallpox and varicella [71]. A call was issued in the recent past for dental surgeons, alongside physicians, to consider monkeypox as a differential diagnosis during the outbreak, owing to the increasing manifestation of lesions in the oral cavity [72].

9. Diagnosis

In regions most affected by Clade I mpox, diagnosis is often based on clinical assessment due to limited diagnostic capacity and the availability of point-of-care tests. This clinical diagnosis can be challenging due to the similarity between mpox lesions and those associated with varicella (chickenpox) [74]. Serological techniques like Enzyme-linked immunosorbent assay (ELISA) is employed to detect IgM and IgG antibodies specific to monkeypox virus in patient serum, typically appearing around 5 days (IgM) and 8 days (IgG) after infection. A four-fold increase in these antibody levels can support the diagnosis of monkeypox during both acute and recovery phases. However, ELISA has limited specificity because of potential cross-reactions with other poxviruses, which reduces its effectiveness for direct virus identification. Consequently, while ELISA is useful for epidemiological research, it is not the most reliable method for definitive monkeypox diagnosis. Similarly, electron microscopy, which detects viral particles, is not fully reliable for the monkeypox virus due to the challenge of distinguishing it from other poxviruses based on morphology alone [27].

Real-time polymerase chain reaction (RT-PCR) is a genetic technique used to detect monkeypox virus (MPXV) by targeting conserved regions in specific genes. These include the extracellular envelope protein gene (B6R), DNA polymerase gene (E9L), DNA-dependent RNA polymerase subunit 18 (RPO18), and complement binding protein genes (C3L, F3L, and N3R). Additionally, other methods such as recombinase polymerase amplification (RPA), loop-mediated isothermal amplification (LAMP), and restriction length fragment polymorphism (RFLP) have been developed for MPXV DNA detection [75]. The World Health Organization (WHO) recommends that confirmation of monkeypox virus infection should be achieved through nucleic acid amplification testing (NAAT). This involves the use of real-time or conventional polymerase chain reaction (PCR) to detect unique viral DNA sequences. PCR may be employed as a standalone method or in conjunction with sequencing techniques [69]

10. Treatment

For the majority of patients with mpox who possess intact immune systems and lack skin conditions, supportive care and pain management are usually adequate for recovery without the need for specific medical treatment. Conversely, those who are severely immunocompromised or have particular skin conditions, such as eczema, face an increased risk of uncontrolled viral transmission and may develop severe, potentially life-threatening complications associated with mpox [17]. Currently, no specific treatment is approved for monkeypox. However, several antiviral medications used for smallpox and related conditions might be effective. These include:

- √ **Tecovirimat (TPOXX):** An antiviral developed for smallpox treatment.
- √ **Brincidofovir (Tembexa):** Another antiviral for smallpox.
- √ **Cidofovir (Vistide):** An intravenous antiviral used to treat cytomegalovirus retinitis in AIDS patients.

Additionally, intravenous vaccinia immune globulin (VIGIV), which is approved for treating complications from smallpox vaccination, may be authorized for use against monkeypox during outbreaks. The National Institute of Allergy and Infectious Diseases (NIAID) has been instrumental in developing tecovirimat and brincidofovir [76].

11. Prevention and Control

There have been several approaches taken in the fight to stop the monkeypox from spreading. The main goal in terms of ecology should be to reduce human exposure to possible host species. This can be accomplished by encouraging vegetarian substitutes and reducing reliance on specific hosts, especially rodents, as a source of protein [77]. Vaccinating susceptible populations, including healthcare personnel, individuals who come into contact with monkeypox virus patients, and those employed in remote places, is another crucial strategy. Since smallpox vaccinations have been successful in eliminating smallpox and other harmful viral zoonoses that are re-emerging, the CDC advises utilizing them for this purpose. However, due to possible dangers, people with weakened immune systems should refrain from receiving the smallpox vaccine [78].

Preventing human-to-human transmission of monkeypox requires strict infection control measures, such as the use of gloves, protective clothing, surgical masks, and properly trained healthcare staff. Patients showing symptoms of monkeypox should be placed in isolation preferably in a negative pressure room or, if not available, a private room. Preventive measures should address risks associated with droplets, direct contact, and overall exposure. Furthermore, in wealthier countries, enhancing awareness among healthcare professionals about monkeypox and its endemic regions is a vital

preventive measure [61]. In a very recent move, the WHO prequalified Bavarian Nordic's MVA-BN as the first vaccine for Mpox [79].

12. Conclusions and Recommendations

Monkeypox, a re-emerging zoonotic disease, has seen a troubling resurgence with outbreaks expanding beyond its traditional African regions, notably with Clade IIb and increased human-to-human transmission, especially among men who have sex with men. The disease presents varied clinical symptoms, including fever, rash, and potentially severe complications such as pneumonitis and encephalitis. Diagnostic challenges persist, requiring advanced serological, molecular, and imaging techniques, while treatment options remain limited, with smallpox antivirals offering partial efficacy. To address these challenges, there is an urgent need for enhanced surveillance, expanded vaccination efforts, public awareness campaigns, rigorous infection control measures, and continued research. Global collaboration and a focus on socio-economic and environmental factors are essential for effectively managing and mitigating the impact of monkeypox outbreaks.

Based on the above conclusion the following recommendations were forwarded:

- √ Strengthen surveillance systems to monitor monkeypox cases more effectively, particularly in both endemic and non-endemic regions.
- √ Implement targeted vaccination campaigns, especially in high-risk populations and regions with ongoing outbreaks.
- √ Increase public awareness about monkeypox, focusing on symptoms, transmission routes, and preventive measures.
- √ In healthcare settings, enforce strict infection control practices, including the use of personal protective equipment (PPE) and isolation protocols for infected patients.
- √ Emphasis is given to the development of safe, effective, and low-cost chemotherapeutic agents as well as vaccines that can be easily afforded by the poor resource nations.

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Contribution of Authors

All the authors contributed equally.

Conflict of Interest

There was no conflict of interest among the authors.

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