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Mini-Narrative Review

The resurgence of monkeypox: Epidemiology, clinical features, and public health implications in the post-smallpox eradication era

Parminder Singh [a,1], Sathvik Belagodu Sridhar [b], Javedh Shareef [c], Sirajunisa Talath [d], Priyanka Mohapatra [a,1], Mahalaqua Nazli Khatib [e,1], Suhas Ballal [f], Mandeep Kaur [g], Deepak Nathiya [h], Shilpa Sharma [i], G.V. Siva Prasad [j], Aashna Sinha [k], Amit Varma [l], Ganesh Bushi [m], Abhay M. Gaidhane [n], Prakasini Satapathy [o,p], Muhammed Shabil [q], Renu Sah [r], Jaffar A. Al-Tawfiq [s,t,u,1], Ranjit Sah [v,w,x,*,1], Alfonso J. Rodriguez-Morales [y,z,1]

[a] Evidence for Policy and Learning, Global Center for Evidence Synthesis, Chandigarh, India
[b] RAK College of Pharmacy, RAK Medical & Health Sciences University, Ras Al Khaimah, 11172, United Arab Emirates
[c] Dept of Clinical Pharmacy & Pharmacology, RAK College of Pharmacy, RAK Medical & Health Sciences University, Ras Al Khaimah, 11172, United Arab Emirates
[d] Dept of Pharmaceutical Chemistry, RAK College of Pharmacy, RAK Medical & Health Sciences University, Ras Al Khaimah, 11172, United Arab Emirates
[e] Division of Evidence Synthesis, Global Consortium of Public Health and Research, Datta Meghe Institute of Higher Education, Wardha, India
[f] Department of Chemistry and Biochemistry, School of Sciences, JAIN (Deemed to Be University), Bangalore, Karnataka, India
[g] Department of Sciences, Vivekananda Global University, Jaipur, Rajasthan, 303012, India
[h] Department of Pharmacy Practice, Institute of Pharmacy, NIMS University, Jaipur, India
[i] Chandigarh Pharmacy College, Chandigarh Group of Colleges-Jhanjeri, Mohali, 140307, Punjab, India
[j] Department of Chemistry, Raghu Engineering College, Visakhapatnam, Andhra Pradesh, 531162, India
[k] Uttaranchal Institute of Pharmaceutical Sciences, Division of Research and Innovation, Uttaranchal University, India
[l] Department of General Medicine, Graphic Era (Deemed to Be University), Clement Town, Dehradun, India
[m] School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India
[n] Jawaharlal Nehru Medical College, and Global Health Academy, School of Epidemiology and Public Health. Datta Meghe Institute of Higher Education, Wardha, India
[o] Center for Global Health Research, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India
[p] Medical Laboratories Techniques Department, AL-Mustaqbal University, 51001, Hillah, Babil, Iraq
[q] University Center for Research and Development, Chandigarh University, Mohali, 140413, Punjab, India
[r] Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, 160012, India
[s] Specialty Internal Medicine and Quality Department, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia
[t] Infectious Disease Division, Department of Medicine, Indiana University School of Medicine, Indiana, USA
[u] Infectious Disease Division, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[v] SR Sanjeevani Hospital, Kalyanpur, Siraha, 56517, Nepal
[w] Department of Microbiology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Dr. D. Y. Patil Vidyapeeth, Pune, 411018, Maharashtra, India
[x] Department of Public Health Dentistry, Dr. D.Y. Patil Dental College and Hospital, Dr. D. Y. Patil Vidyapeeth, Pune, 411018, Maharashtra, India
[y] Faculty of Health Sciences, Universidad Científica Del Sur, Lima, 15067, Peru
[z] Gilbert and Rose-Marie Chagoury School of Medicine, Lebanese American University, Beirut, 1102, Lebanon

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ABSTRACT

The recent global resurgence of Mpox (formerly monkeypox), primarily transmitted via close contact and respiratory droplets, highlights a significant shift in its epidemiology, particularly among men who have sex with men (MSM). This resurgence underscores the need for robust public health responses and improved surveillance. This comprehensive review of current literature focuses on recent outbreaks, virology, and available treatments.

* Corresponding author. RAK College of Pharmacy, RAK Medical & Health Sciences University, Ras Al Khaimah, 11172, United Arab Emirates.
E-mail addresses: Parminderd965@gmail.com (P. Singh), sathvik@rakmhsu.ac.ae (S.B. Sridhar), javedh@rakmhsu.ac.ae (J. Shareef), sirajunisa@rakmhsu.ac.ae (S. Talath), priyanka.mohapatraa@gmail.com (P. Mohapatra), nazlikhatib@dmiher.edu.in (M.N. Khatib), b.suhas@jainuniversity.ac.in (S. Ballal), mkphd2024@gmail.com (M. Kaur), dnathiya@nimsuniversity.org (D. Nathiya), shilpa2410.research@cgcjhanjeri.in (S. Sharma), sivaprasad.gv@raghuenggcollege.in (G.V. Siva Prasad), aashna07sinha@gmail.com (A. Sinha), amitverma.geims@geu.ac.in (A. Varma), ganeshbushi313@gmail.com (G. Bushi), abhay.psm@dmiher.edu.in (A.M. Gaidhane), Prakasini.satapathy@gmail.com (P. Satapathy), mohdshabil99@gmail.com (M. Shabil), renu.sah4u@gmail.com (R. Sah), jaltawfi@yahoo.com, jaffar.tawfiq@jhah.com (J.A. Al-Tawfiq), ranjitsah57@gmail.com (R. Sah), arodriguezmo@cientifica.edu.pe, alphonso.morales@lau.edu.lb (A.J. Rodriguez-Morales).
[1] Equally contributed as first author.

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Epidemiological data were gathered from various international health reports and analysed to understand transmission dynamics and outbreak patterns. Mpox, characterised by symptoms like fever and rash, has shown variable clinical presentations, particularly among immunocompromised individuals. Recent outbreaks have prompted the development of new diagnostic methods and treatments, including antivirals like Tecovirimat and vaccines such as MVA-BN. Studies have demonstrated the effectiveness of these vaccines in preventing infection, which is crucial for outbreak containment. The global response to the Mpox resurgence requires integrated strategies combining vaccination, antiviral treatments, and public health policies tailored to high-risk populations. Future efforts should focus on vaccine distribution equity and enhancing diagnostic capabilities to effectively manage and mitigate the impact of Mpox.

1. Introduction

Monkeypox (Mpox) has re-emerged as a global health concern, especially in the post-smallpox eradication era, where routine smallpox vaccinations are no longer administered, reducing the incidental immunity that had previously controlled Mpox outbreaks [1,2]. The resurgence of Mpox, particularly noted in the 2022 multi-country outbreak, has been characterised by a notable shift in epidemiology and transmission dynamics, primarily affecting men who have sex with men (MSM). This demographic shift highlights the virus's capability to exploit socio-behavioural factors, necessitating a robust public health response tailored to the affected populations [3,4]. Historically, Mpox was first identified in humans in the 1970s in the Democratic Republic of Congo. Since then, it has been chiefly confined to Central and West Africa, where zoonotic transmission from animals such as rodents and primates was common [5,6]. However, the virus global spread has brought it into new territories where human-to-human transmission is becoming increasingly efficient. This shift has been facilitated by changes in human behaviour, international travel, and possibly viral evolution, which may enhance the virus's transmissibility [7].

Typical clinical manifestations of Mpox begin with flu-like symptoms followed by a characteristic rash, progressing from macules to pustules [8]. However, recent outbreaks have reported atypical presentations, particularly in immunocompromised individuals, complicating timely diagnosis and management [9]. This variability in clinical presentation underscores the need for heightened surveillance, enhanced diagnostic capabilities, and flexible public health strategies to address the changing epidemiology of the disease [10]. Diagnostic efforts have been advanced by developing real-time PCR tests, which remain the gold standard for Mpox detection. Nevertheless, these methods are complemented by serological testing for epidemiological studies, though their utility is limited in acute diagnostics due to cross-reactivity with other orthopoxviruses. In addition, after at least 45 years, antibodies produced by the smallpox vaccination cross-react with and neutralise the Mpox virus in vitro [11]. The advent of newer diagnostic tools, including rapid tests, offers hope for quicker and more accessible diagnostics, which are crucial during outbreaks to enable rapid containment measures [12]. For example, a real-time qualitative PCR assay showed promising results for the rapid diagnosis of Mpox [13]. In the United States, it was recommended to have a non-variola Orthopoxvirus [NVO] assay [14]. Treatment for Mpox has primarily relied on antivirals like Tecovirimat and supportive care. Recent research focused on developing new treatment modalities, including the repurposing of smallpox vaccines and the exploration of new antiviral agents that could offer more targeted and effective management strategies for Mpox [15]. The Modified Vaccinia Ankara - Bavarian Nordic (MVA-BN) vaccine has been a cornerstone in preventive strategies, particularly among high-risk groups. The effectiveness of this vaccine, alongside public health measures like contact tracing and isolation, has been pivotal in controlling outbreaks [16].

Public health responses have increasingly emphasised the importance of community engagement and education to combat stigma and misinformation associated with Mpox. Digital contact tracing and surveillance tools have also been integrated into public health strategies, enhancing the capacity to track and manage outbreaks effectively. These tools, along with traditional public health measures, form the backbone of the response to Mpox, aiming to reduce transmission and mitigate the impact of the virus on affected populations [17]. Moreover, the One Health approach has been recognised as critical in addressing the zoonotic dimensions of Mpox [18]. This approach integrates human, animal, and environmental health strategies to prevent spillover events and control outbreaks at their source. Effective management of Mpox thus requires encompassing medical, veterinary, and environmental sciences to develop holistic strategies that address all aspects of the virus's transmission and control [19].

This review provides a comprehensive analysis of the evolving epidemiology of mpox, blending historical data with contemporary outbreaks to offer a holistic view of the disease's progression. It highlights the latest state-of-the-art diagnostic and therapeutic advancements, emphasising the need for ongoing surveillance, flexible approaches, and cross-border cooperation to effectively contain outbreaks and protect global health from the enduring threat of Mpox.

2. Historical context and recent outbreaks

Mpox, caused by the monkeypox virus (MPVX), a member of the Orthopoxvirus genus, initially emerged in human populations in the 1970s in the Democratic Republic of Congo. Since then, it has remained primarily in Central and West Africa, with sporadic outbreaks occurring outside these regions. The virus has similarities to the variola virus, the causative agent of smallpox, which explains why past smallpox vaccinations have provided some level of immunity against Mpox. Historical data indicate that Mpox was primarily transmitted to humans from animals such as rodents and primates, with human-to-human transmission being less efficient [20]. The recent global resurgence of Mpox, particularly noted in 2022, marked a significant shift in the epidemiology of the disease. Unlike previous outbreaks, the 2022–2023 surge involved widespread transmission among men who had sex with men (MSM), suggesting a potential change in the virus's transmission dynamics [21]. This outbreak highlighted the need for increased surveillance, better diagnostic capabilities, and targeted public health interventions. Recent studies have emphasised the challenges and responses during these outbreaks, as well as discussed the surge of cases in Africa and the lack of vaccine access, and the effectiveness and safety of the MVA-BN vaccine during the outbreak in the United States of America (USA) [22,23].

The global Mpox outbreak prompted the World Health Organization (WHO) to declare a Public Health Emergency of International Concern on July 23, 2022 [24]. Between January 1, 2022, and August 22, 2024, the World Health Organization (WHO) received reports of 102,997 laboratory-confirmed cases of Mpox, alongside 223 deaths, spanning 121 countries within all six WHO regions. The data from July 2024 alone revealed 1425 new cases and six fatalities across 35 countries, underscoring the persistent global transmission of Mpox. Moreover, the distribution of cases in June by WHO showed that the African Region reported 567 cases, markedly higher than its counterparts: the Region of the Americas with 175 cases, the European Region with 100 cases, the Western Pacific Region with 81 cases, and the South-East Asia Region with merely 11 cases. This distribution reinforces the entrenched epidemiological footprint of mpox within African territories as opposed

to its episodic appearances elsewhere. There were no reported cases in the Eastern Mediterranean region during this period, highlighting a geographical variance in the incidence of the disease [25]. Four new Eastern African nations—Burundi, Kenya, Rwanda, and Uganda—reported their first cases of Mpox in July 2024 [26]. Especially in the Democratic Republic of Congo, there has been a significant increase in the report of cases, even higher than in 2022/2023, reaching the highest peaks over the May–August weeks of 2024 (Fig. 1).

Using a timeline approach, the scatter plot shows the sampling dates of disease cases in different nations. Every nation is depicted by a distinct hue, with data points dispersed across 2017 and 2023. Clearly illustrates the expansion of sample and monitoring initiatives over time, especially in the United States, Brazil, and many European countries (Fig. 2a). The escalated sampling in these regions could be interpreted as a response to local outbreaks or as part of enhanced global surveillance measures. The data here underscores the importance of continuous monitoring, as increased sampling is often correlated with detecting new cases or variants, enabling timely public health responses. Geographical visualisation of the monkeypox cases, utilising varying-sized circles to indicate the number of cases in different regions (Fig. 2b). The use of proportional circles helps in quickly identifying areas with the highest disease burden, which are notably in Central and Western Africa and parts of Europe. This geographical distribution is crucial for understanding regional differences in disease spread and can assist in allocating resources effectively to areas with higher transmission rates. The phylogenetic trajectory of the monkeypox virus illustrates the accumulation of mutations across various lineages over time (Fig. 2c). The phylogenetic tree not only details the evolutionary dynamics of the virus but also indicates a continuous diversification of genetic lineages, marked by specific sub-lineages such as A.1, A.2, A.3, and B.4.3. The progressive increase in mutations shown in this panel is vital for identifying potentially virulent strains and can guide the development of targeted vaccines and therapies [27].

A concerted effort has been made to enhance research in response to recent outbreaks. Studies are focused on understanding the viral genomics, pathogenesis, and immune response to the virus. For instance, Bleichrodt et al. evaluate epidemic forecasting models, which are crucial for planning public health responses to outbreaks. This study, along with others, highlights the importance of developing robust forecasting and surveillance systems to manage and mitigate the impact of the virus effectively [28].

3. Epidemiology

The epidemiology of the Mpox virus encompasses a broad and complex landscape of transmission dynamics, reservoir hosts, zoonotic potential, and risk factors for human infection (Fig. 2). Understanding these aspects is crucial for controlling outbreaks and preventing the spread of the virus. Mpox primarily spreads through close, personal, often skin-to-skin contact, including direct contact with Mpox rash, scabs, or body fluids from an infected person [29]. Transmission can also occur by respiratory secretions during prolonged, face-to-face contact or touching items recently contaminated by patient fluids or lesion materials [30,31]. Recent outbreaks highlight the virus's ability to spread within dense networks, particularly among MSM, emphasising the importance of targeted public health interventions [32–34]. Furthermore, Schwartz's study on the impact of Mpox among pregnant women during the 2023–2024 outbreak in the Democratic Republic of Congo provides a poignant example of the severe outcomes associated with the virus. This study highlights the high rates of miscarriage and stillbirth among infected pregnant women, illustrating the critical need for effective disease management and support for vulnerable populations during outbreaks [35].

Mpox is a zoonotic virus with rodents and primates suspected as potential reservoirs, particularly in endemic regions such as Central and West Africa. The virus can jump from animals to humans, with initial transmission likely occurring through handling infected animals or consuming wild game. The zoonotic nature of Mpox underscores the need for vigilant monitoring of animal populations and minimising human-wildlife conflict to prevent spillover events [32]. Wastewater surveillance to detect MPXV in Brazil showed the potential of sewage surveillance as a robust public health tool for monitoring not only Mpox but also other co-circulating viruses [36].

Risk factors for Mpox infection include close physical contact with infected individuals or contaminated materials. Healthcare workers, household members, and sexual partners of infected individuals are at higher risk [37]. Since the 2022–2023 multi-country outbreak, sexual contact remains the predominant mode of transmission, accounting for 83.8 % (19,102 out of 22,801 cases) of reported cases, followed by non-sexual person-to-person contact. This trend continued over the past

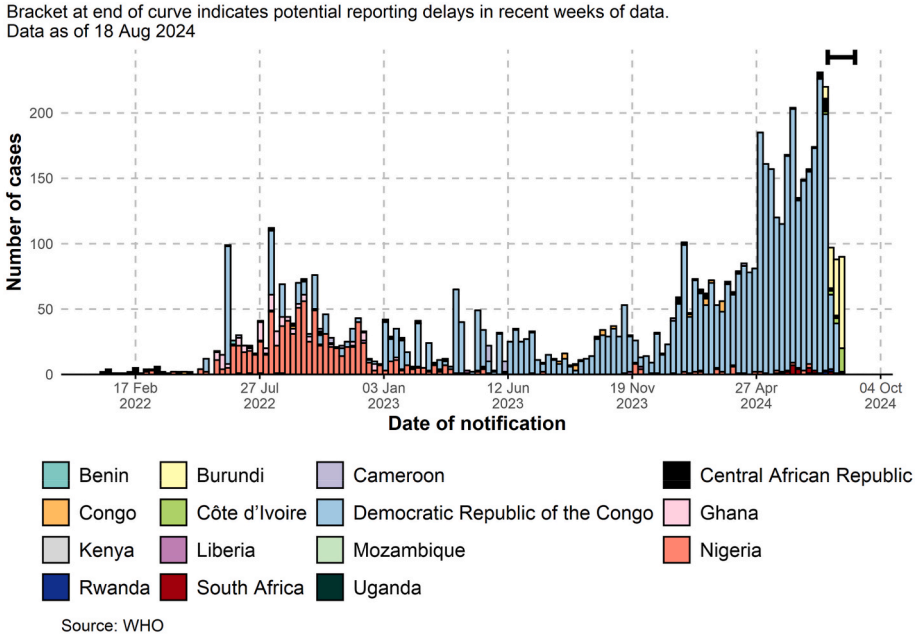

Fig. 1. Number of Mpox cases per week in the African region of WHO during 2022–2024. From: WHO (https://worldhealthorg.shinyapps.io/mpx_global/).

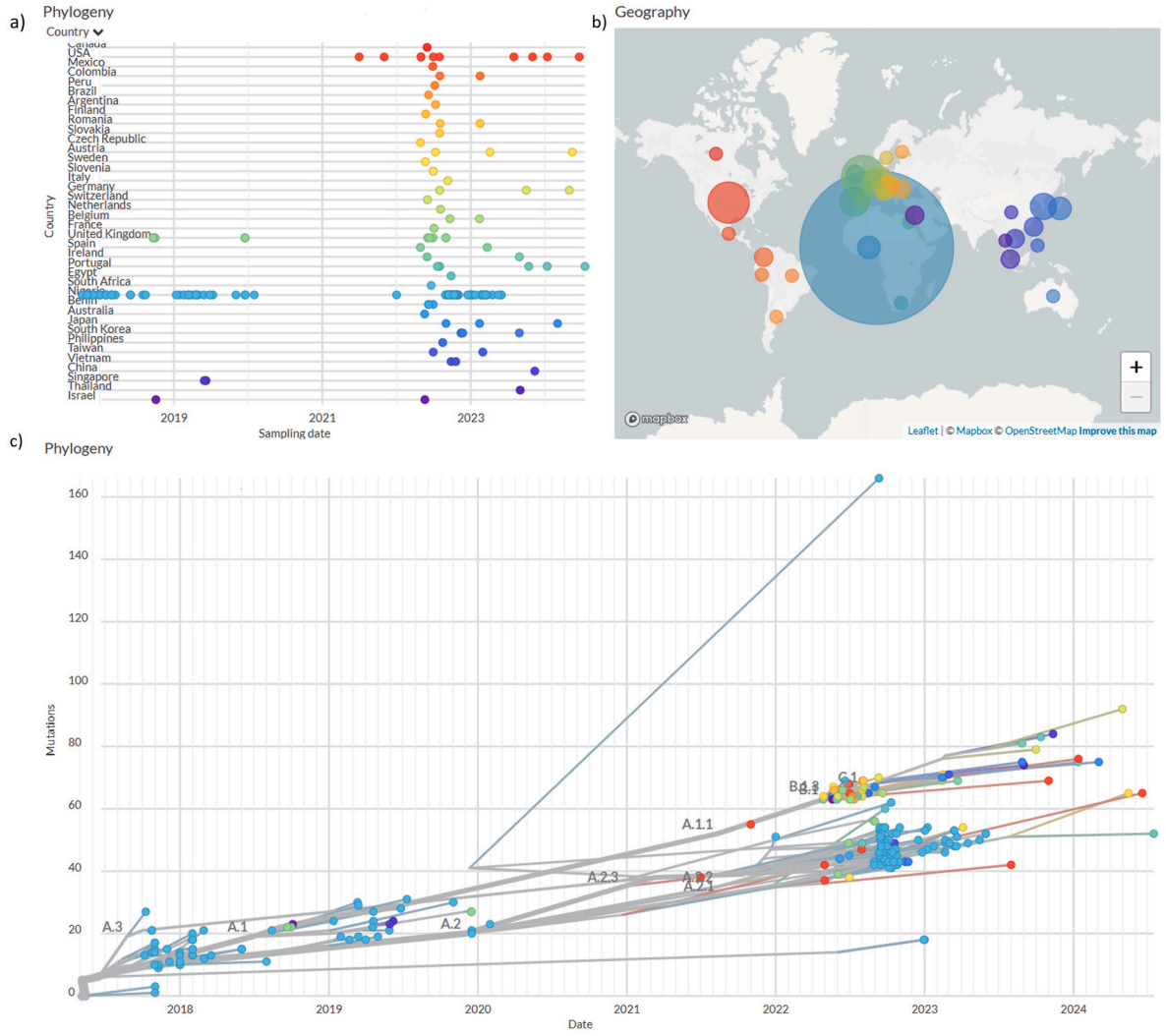

Fig. 2. Global Dispersal and Phylogenetic Development of the Monkeypox Virus Clade IIb from 2017 to 2024 (Source: Nextstrain image). a) Phylogeny Over Time by Country. b) Geographic Distribution of Cases. c) Phylogenetic Lineages Over Time.

six months, with sexual contact being reported in 95.6 % (483 out of 505) of the newly recorded cases [25]. Recent data also indicate that certain social behaviours and large gatherings can facilitate rapid transmission, particularly in non-endemic regions where natural immunity may be lower [38]. Stigma and social inequalities can exacerbate transmission by hindering effective public health responses and access to care [39,40]. Studies suggest that changes in human behaviour, increased global travel, and ecological disruptions may contribute to the broader geographic spread of the virus [39,41]. Public health strategies focusing on surveillance, community engagement, and education about transmission are crucial for managing and controlling Mpox [42,43].

The surveillance and reporting mechanisms for Mpox play a critical role in the global public health response to the disease. As outlined in WHO's interim guidance, surveillance efforts are essential for detecting outbreaks, containing transmission, and progressing toward the elimination of Mpox [44]. Countries are urged to rapidly identify Mpox cases through clinical examination and laboratory testing, adhering to the International Health Regulations (2005) and the mpox standing recommendations issued by the WHO Director-General (August 2023) [45]. The surveillance systems must include reporting of probable and confirmed cases to WHO through national focal points, with minimum datasets that encapsulate epidemiologically relevant information [44]. Diagnostic criteria for Mpox have evolved to incorporate a broad spectrum of laboratory techniques, including PCR testing of lesion samples, which remains a cornerstone for confirmation [13]. The definitions for suspected, probable, and confirmed cases are meticulously structured to facilitate precise surveillance and ensure robust data collection, reflecting the variable clinical presentations of Mpox across different regions [46]. Such systematic surveillance and nuanced diagnostic criteria are pivotal for implementing specific public health interventions and for global monitoring of the disease's epidemiology.

4. Virology and pathogenesis

The genomic structure of the monkeypox virus (MPXV), shown in Fig. 3, is complex and comprises several unique features such as surface tubules, the outer membrane, lateral bodies, the palisade layer (core membrane), core fibrils, and the virus's double-stranded DNA core. MPXV belongs to the Orthopoxvirus genus, which includes well-known viruses such as smallpox and vaccinia. The virus has a large double-stranded DNA genome, which encodes for numerous proteins that play crucial roles in its lifecycle, immune evasion, and virulence [47]. One of the significant features of the MPXV genome is the terminal regions, which contain genes that modulate the host immune response. These regions are notably diverse and are critical to the virus's ability to infect multiple hosts. However, the central region of the genome is more conserved and encodes essential viral replication and structural proteins [48]. Recent studies have shed light on specific proteins encoded by the

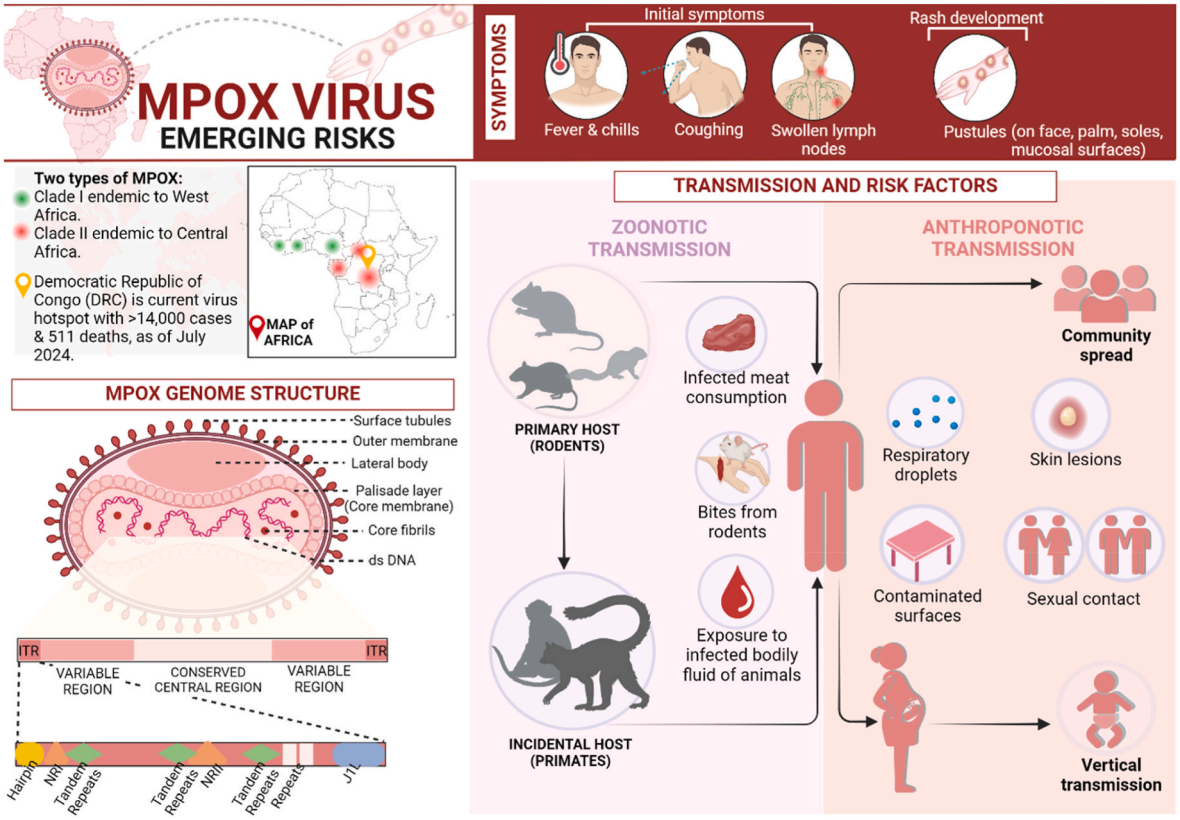

Fig. 3. Mpox virus: Transmission, symptoms, and genomic structure.

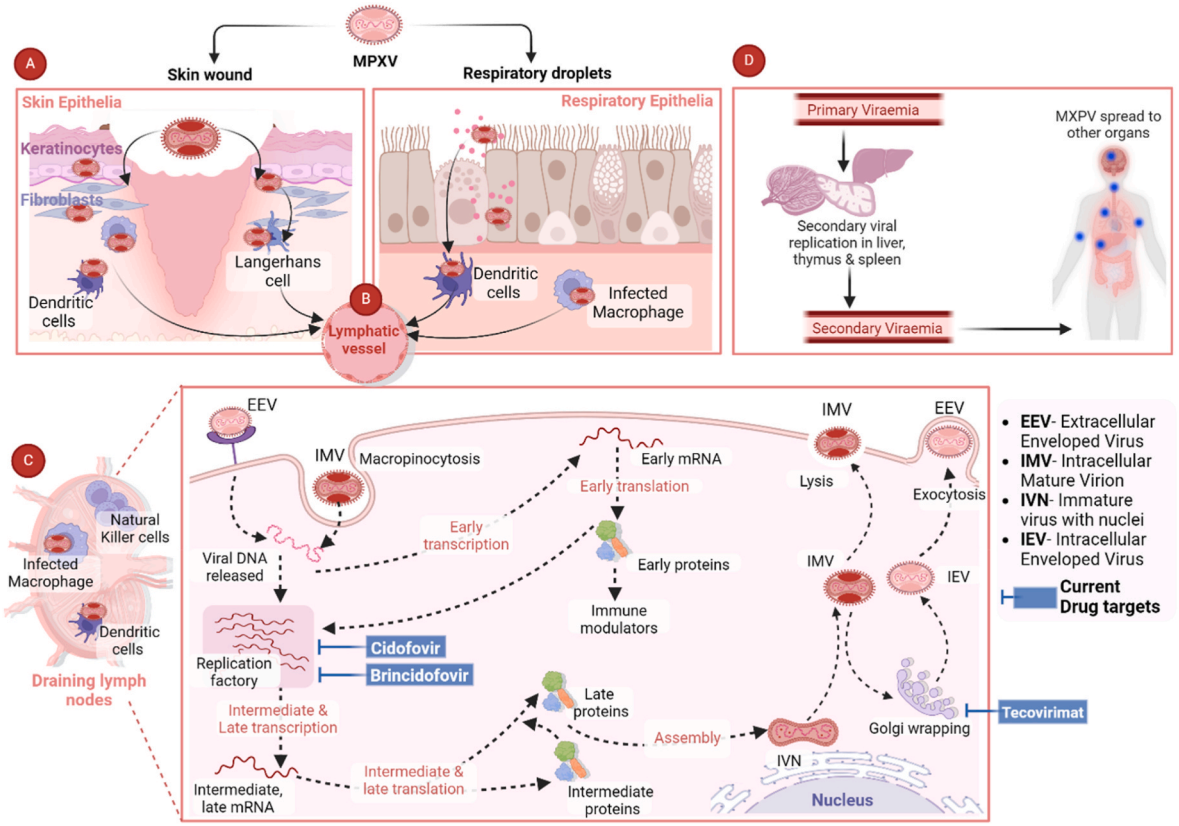

Fig. 4. Comprehensive overview of monkeypox virus infection pathways and antiviral intervention points.

MPXV genome [7,49,50]. For instance, the poxin enzyme, which is crucial for overcoming host immune defences, has been detailed in structural studies. Poxin acts by cleaving 2′-3′-cGAMP, a critical molecule in the cGAS-STING pathway of the host's innate immune system [51]. The detailed crystal structure of poxin revealed its conserved beta-sheet fold and the critical residues involved in its function, underscoring potential targets for antiviral drug development [52]. Another critical area of study has been the MPXV A41L gene, which encodes a secreted protein that interacts with host chemokines to modulate the immune response. The A41 protein does not bind strongly to actin or poly (L-proline), distinguishing it from similar proteins in other viruses and suggesting unique interactions with the host's immune system [53]. Further analysis has also been conducted on the MPXV DNA polymerase holoenzyme complex, which is essential for viral DNA replication. The structure of this complex, resolved using cryo-electron microscopy, revealed a "forward sliding clamp" mechanism, highlighting similarities and differences with DNA polymerases from other organisms, which could guide antiviral drug design [49].

The virus first infects keratinocytes, dendritic cells, fibroblasts, and Langerhans cells in the skin or macrophages and dendritic cells in the respiratory system. Fig. 4 (Panel A) depicts the virus interacting with skin or respiratory epithelia. This interaction highlights the virus's ability to enter the body through several cell types and cause local infection [54]. Following the initial infection, MPXV is transported by lymphatic pathways to the draining lymph nodes, as shown in Fig. 4 (Panel B). This is a crucial stage in the virus's systemic spread when infected macrophages and dendritic cells help the virus travel to other body areas. The development of primary viremia leads to the primary lymphatic spread of the virus. Consequently, it infects other crucial organs, such as the liver, spleen, and thymus, where secondary viral replication occurs. The secondary viremia then follows, disseminating the virus to distant organs, including the lungs, kidneys, and intestines. This final spread can lead to widespread organ involvement and increased disease severity, as depicted in Fig. 4 (Panel D) [55].

The replication and host cell entry mechanisms of the Mpox virus are crucial for understanding its pathogenesis and for developing targeted treatments and preventive measures. The Extracellular Enveloped Virus (EEV) and the Intracellular Mature Virion (IMV) are crucial stages of the virus lifecycle. IMV and EEV exhibit distinct structural differences in their surface glycoproteins and envelope membranes. IMV has a single membrane and is released upon cell lysis, entering host cells through direct fusion and endocytosis. In contrast, EEV features a double-membrane structure and gains entry into host cells primarily through membrane fusion [56]. MPXV enters host cells predominantly through macropinocytosis, which involves engulfing the virus by the host cell membrane to form an internal cyst, as shown in Fig. 4 (Panel C). This method may be accompanied by other entry mechanisms, such as clathrin-mediated endocytosis, although specific cellular receptors involved in MPXV entry have not been definitively identified [57,58]. Once inside the host cell, MPXV is transported to the cytoplasm, where the viral core uncoats, releasing viral DNA and enzymes necessary for initiating the replication process. MPXV is unique among viruses as it replicates entirely in the host cell's cytoplasm, utilising its own viral DNA-dependent RNA polymerase to bypass the host's nuclear machinery. This replication begins with the transcription of early viral genes responsible for synthesising replication enzymes and proteins that modulate the host immune response [59].

Subsequent viral DNA replication occurs in specialised structures within the cytoplasm known as viral factories. These factories are essential for synthesising late viral genes, which encode structural proteins crucial for new virion assembly. The assembly process culminates in the encapsulation of viral DNA within protein shells, forming complete virions ready to infect additional cells [49]. Finally, mature virions are released from the host cell either through cell lysis, which results in cell death, or through non-lytic processes like budding, which allows the virus to continue spreading without immediately killing the host cell. Throughout its lifecycle, MPXV employs numerous strategies to evade the host immune system, such as producing proteins that inhibit the host's interferon response, thereby enhancing viral survival and propagation [58,60]. Several phases of this lifecycle are targeted by current pharmacological therapies like Tecovirimat, Brincidofovir, and Cidofovir to prevent viral reproduction and dissemination [61].

5. Phylogenetic analysis

The NCBI virus taxonomy database provided the protein and nucleotide sequence for the monkeypox (taxid-10244) virus to perform a pairwise similarity analysis. Based on the following parameters, we selected 78 protein sequences from 1,260,435 total protein sequences and downloaded their CDS for analysis: host homo-sapiens; protein B22R protein family; date: January 01, 2024 to August 17, 2024; and geographic location: Asia, Africa, and Europe. Only 60 sequences were remaining for examination after deleting sequences that had missing residues [62]. The B22R protein is implicated in immune evasion by interacting with host immune factors, such as interferons [63]. Using MEGA11's default parameters, the MUSCLE program completed the sequence alignment. Phylogenetic analysis was carried out in Mega11 using the Maximum Likelihood technique (50 Bootstrap replication) and the Tamura-Nei model as a replacement model [64,65]. The phylogenetic tree with the highest log likelihood (−7890.11) is shown in Fig. 5.

The tree depicts several distinct clades, with a notable differentiation between the DRC and Germany sequences. This suggests geographical segregation in the viral strains, potentially due to evolutionary pressures specific to each region. The sequences from the DRC (Democratic Republic of the Congo) are more varied, highlighted by multiple sub-clades that suggest a richer genetic diversity in this region. This diversity could be attributed to the extended presence and possibly higher virus transmission rates within local populations. In contrast, the sequences from Germany are grouped more tightly, which might indicate a more recent introduction of the virus into this region or less genetic variation due to a bottleneck effect during transmission. Other sequences from Portugal and China within the German clades suggest possible travel-related introductions of the virus into Europe. The coloured nodes, varying from red to blue, indicate specific genetic markers or mutations of interest. These mutations might be pivotal in understanding the adaptation of the virus in different hosts or its response to environmental pressures. For instance, the red nodes might represent a mutation that confers a survival advantage in non-endemic regions like Germany and Portugal or resistance to possible treatments or vaccines. This phylogenetic analysis helps identify potential zoonotic transmission events, track the spread of the virus across borders, and monitor the emergence of new variants that could influence the course of outbreaks. For instance, understanding that certain strains are confined to specific regions can help tailor vaccines and effective treatments against the prevalent strains in those areas.

6. Clinical presentation

The clinical presentation of Mpox are characterised by a diverse range of symptoms and a progression that can vary significantly between individuals, particularly in the face of recent outbreaks. The typical onset of Mpox involves flu-like symptoms such as fever, headache, muscle aches, and fatigue, followed by a distinct rash [66]. The rash progresses through several stages, from macules to papules, vesicles, pustules, and crusts. The distribution of the rash is usually widespread, affecting the face, palms, and soles more frequently than seen in similar diseases like chickenpox [67]. In severe cases, the rash can cover large areas of the body, causing significant discomfort and complications [68]. Although that, during the 2022/2023 epidemics, the clinical presentation observed included patients showing initially genital lesions without other symptoms [69,70].

However, the emergence of atypical presentations of Mpox was

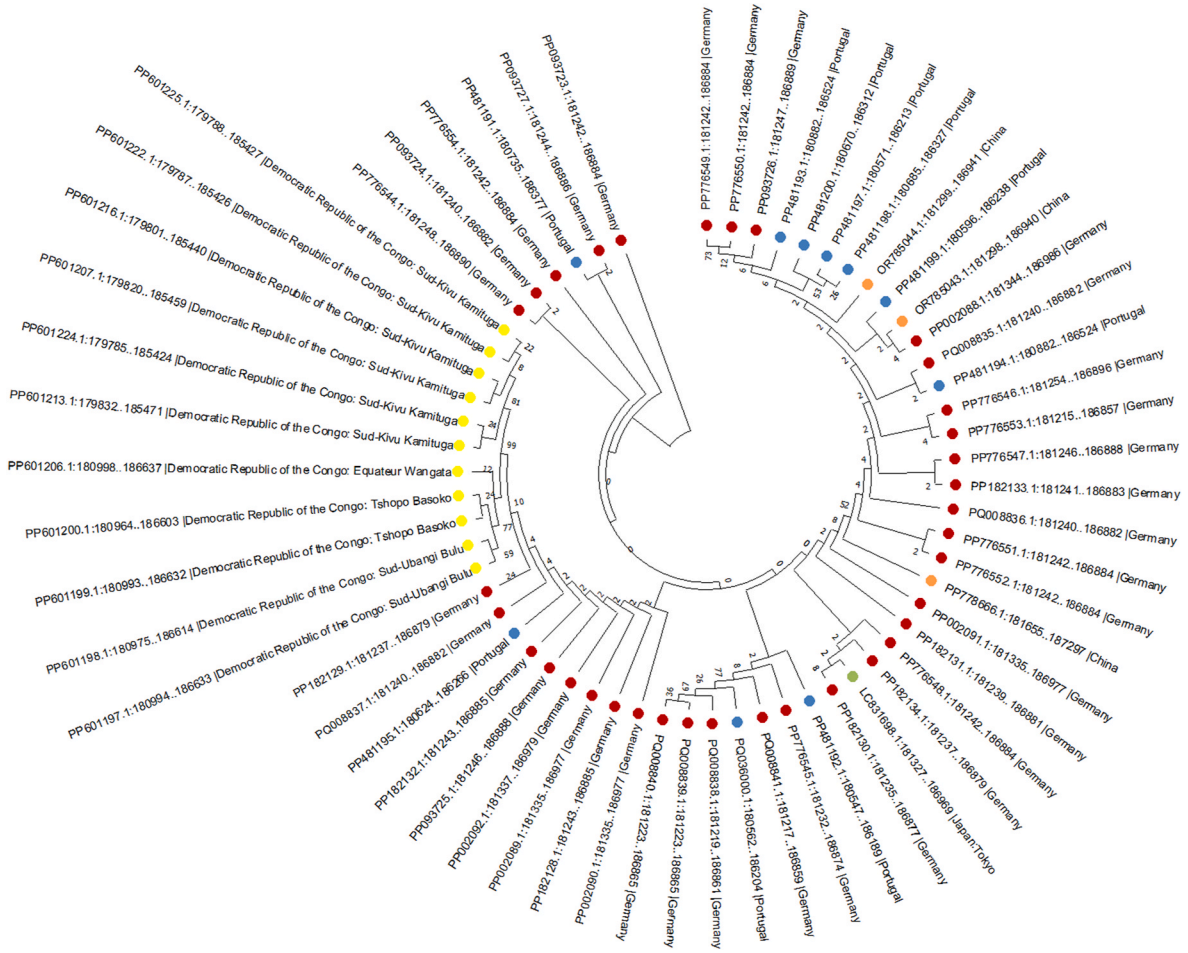

Fig. 5. Phylogenetic analysis of B22R protein variants in mpox virus across different geographical locations.

documented in recent outbreaks, which pose diagnostic challenges and underscore the virus's complexity, particularly in immunocompromised populations [71,72]. For example, some cases have been noted where patients experience severe abdominal pain and proctitis without the typical rash associated with Mpox, complicating timely diagnosis [73]. This has been mainly observed among individuals with HIV, where the virus may trigger more severe systemic symptoms [10]. Furthermore, there have been instances where patients do not exhibit the standard prodromal fever, or the rash appears without preceding flu-like symptoms [74]. In some scenarios, the rash may not progress through the usual stages of macules to pustules, instead presenting in only one form. Such variations can significantly complicate the clinical assessment and timely diagnosis of Mpox. In immunocompromised individuals, these atypical presentations can lead to severe complications, including pneumonia, sepsis, and encephalitis, and in some cases, may result in death [75,76]. The complexity of these presentations requires a nuanced approach to diagnosis and management, emphasising the need for healthcare providers to consider a broad differential diagnosis and utilise comprehensive diagnostic strategies to manage and treat Mpox effectively [77,78].

7. Diagnosis

Diagnosis of Mpox traditionally relies on detecting the virus using polymerase chain reaction (PCR) testing, which remains the most accurate method [79]. PCR can detect Mpox DNA from skin lesions, fluids, and respiratory samples. However, the integration of serological testing can provide additional epidemiological insights, though its use in acute diagnosis is limited due to cross-reactivity with other orthopoxviruses [80]. Diagnostic challenges are often compounded by the need to differentiate Mpox from other infections such as herpes, syphilis, and bacterial skin infections, necessitating a comprehensive approach that includes clinical assessment and laboratory testing [12,81]. Some studies illustrate the complexities of diagnosing Mpox based solely on visual assessments of lesions. This has significant implications for clinical practice and highlights the need for more robust diagnostic tools to operate effectively in resource-limited settings where advanced laboratory facilities are unavailable [82].

Innovations in diagnostic methodologies have significantly improved the detection and management of Mpox. For example, developing real-time PCR-based detection kits has provided high sensitivity and specificity tools, critical during outbreaks to ensure rapid containment measures. These kits have been rigorously evaluated against other diagnostics, confirming their utility in diverse clinical settings [12].

8. Treatment and management

Tecovirimat (TPOXX) is the primary antiviral medication approved for treating Mpox. It effectively reduces the duration and severity of symptoms when administered early in the disease [55]. Tecovirimat inhibits the function of the viral VP37 protein, which is essential for the virus's ability to spread within the host. Several preclinical studies have validated the efficacy of tecovirimat against Mpox [83–85]. In these studies conducted on animals, tecovirimat significantly reduced mortality rates for those exposed to Mpox, ensuring survival rates of at least 90 % [86]. As of January 2022, tecovirimat is the only antiviral authorised by the European Medicines Agency (EMA) in Europe for

treating Mpox and can be used in adults and children who weigh at least 13 kg [61]. Despite its efficacy, tecovirimat is sometimes limited by availability and regulatory approvals in different regions. Other antivirals like cidofovir and brincidofovir are also used, particularly for severe cases, although their use can be associated with significant side effects [68]. Supportive care remains a cornerstone of Mpox management, focusing on alleviating symptoms and preventing secondary infections. This includes the management of pain and itching with analgesics and antihistamines, hydration to manage dehydration, and antibiotics for secondary bacterial infections. Care strategies are tailored to individual symptoms and severity, emphasising monitoring and managing complications such as pneumonia or sepsis, especially in immunocompromised individuals [73].

The ongoing research and development in Mpox treatment are vital for enhancing our ability to combat this virus effectively. As the landscape of Mpox continues to evolve, so too must our approaches to its management and treatment, ensuring that healthcare systems worldwide are prepared to handle outbreaks effectively [87,88].

9. Vaccination and prevention

Research into new treatments for Mpox continues to advance, exploring several promising directions. One significant area of focus is developing new vaccines to protect against Mpox [89,90]. Among the candidates in various stages of research and development are MVA-BN, mRNA-1769, the Bavarian Nordic smallpox vaccine, LC16m8, BNT166a, and JYNNEOS, each representing a unique approach to enhancing immune defence against the disease [91–97]. These vaccines aim not only to prevent infection but also to mitigate the severity of the disease post-exposure. Additionally, monoclonal antibodies and new antiviral agents are being explored to provide more targeted and effective treatment options against Mpox [81]. The recent outbreaks have underscored the need for global access to vaccines and antiviral medications. Strategies to improve the distribution of these resources, particularly in under-resourced settings, are critical. Public health efforts are also focused on educational campaigns to raise awareness about Mpox transmission and prevention strategies, aiming to reduce stigma and encourage timely medical consultation [33].

Historically, the smallpox (vaccinia) vaccine was found to offer significant cross-protection against Mpox due to the close genetic relation between the two Orthopoxviruses [98]. This cross-immunity was a fortunate byproduct of the global smallpox eradication campaign, which concluded in the late 20th century, leaving a legacy of partial immunity in older populations. Research has shown that the smallpox vaccine provides about 85 % effectiveness in preventing Mpox, a fact that has influenced public health strategies against Mpox outbreaks long after smallpox vaccines were discontinued [20]. The landscape of modern Mpox vaccines has expanded significantly from the historical reliance on smallpox vaccines for cross-protection, leading to the development of vaccines specifically targeting Mpox. The primary vaccine currently in use for Mpox is Modified Vaccinia Ankara (MVA-BN), also known as JYNNEOS in the United States, which is a non-replicating vaccine derived from the Vaccinia virus. This vaccine has been carefully developed to avoid the side effects of older vaccinia-based vaccines. It is suitable for a wide range of populations, including immunocompromised ones. Some data indicated that MVA-BN is approximately 85 % effective in preventing Mpox infection, demonstrating high efficacy, mainly when administered before exposure [23].

Another promising candidate is the LC16m8 vaccine, initially developed in Japan as a safer alternative for smallpox vaccination. Recent evaluations suggest that it also offers protection against Mpox, potentially expanding the arsenal against current and future outbreaks. Vaccine access, distribution logistics, and vaccine hesitancy persist despite these advancements, especially in low-resource settings. These challenges necessitate continuous public health efforts to enhance global vaccination strategies, improve public education to combat stigma and ensure equitable vaccine distribution [20].

Effective vaccination strategies are crucial for controlling Mpox outbreaks. These strategies include targeted vaccination of high-risk groups, such as healthcare workers, contacts of Mpox patients, and MSM, who have been disproportionately affected in recent outbreaks. The use of ring vaccination—vaccinating all contacts around a diagnosed case—has proven effective in quickly containing outbreaks within limited communities [99]. Table 1 displays an overview of current vaccine clinical trials, including key study details, interventions, and phases provided by clinicaltrails.gov. In addition to targeted vaccination, public health authorities have also emphasised the importance of community engagement and public education campaigns to combat stigma and spread awareness about the availability and safety of vaccination, thereby enhancing vaccine uptake [39].

Despite these advances, several challenges remain. Vaccine hesitancy, logistical issues in vaccine distribution, and limited global manufacturing capacity can hinder response efforts, particularly in low-resource settings. Future strategies must focus on overcoming these barriers to ensure equitable vaccine access. Additionally, ongoing research into Mpox epidemiology and vaccine efficacy will be crucial to adapt vaccination strategies as the virus evolves and new outbreaks occur. The continued development of Mpox-specific vaccines, coupled with strategic vaccination campaigns, holds the promise of significantly reducing the impact of this virus globally. As with other infectious diseases, the integration of vaccination with broader public health strategies, such as surveillance, education, and international cooperation, will be essential to manage and prevent Mpox effectively [15,100].

10. Public health response and challenges

Effective surveillance systems are essential for early detection and management of Mpox outbreaks. These systems rely on robust data collection and reporting mechanisms that enable health authorities to monitor the spread of the disease in real time. Contact tracing complements surveillance by identifying and monitoring individuals who may have been exposed to the virus, thus preventing further transmission. The integration of innovative technologies, such as digital tracking tools, has enhanced the efficiency of these processes, allowing for rapid response and containment of outbreaks [5,17]. Managing public reactions during an outbreak requires effective risk communication. The public needs to be informed promptly, clearly, and transparent to allay fears, debunk misconceptions, and promote compliance with medical advice. Involving community leaders and stakeholders in the information-dissemination process guarantees that messages are culturally relevant and more palatable to the community. Community engagement is equally vital. Addressing the stigma attached to the illness is another critical component of effective communication tactics, as it can impede efforts to contain the outbreak [101].

Protecting healthcare workers is paramount, as they are at the front line of any outbreak response. Adequate training on adequately using personal protective equipment (PPE) and infection control procedures reduces the risk of virus transmission within healthcare settings. Additionally, healthcare workers must be trained in the specific clinical management of Mpox to provide the best care for patients while protecting themselves. Regular drills and updated training sessions ensure that healthcare teams are prepared to handle cases effectively and safely [102]. These components underscore the complexity of responding to Mpox and highlight the need for a comprehensive approach incorporating advanced surveillance, effective communication, community engagement, and rigorous protection and training for healthcare providers.

11. One Health approach to mpox control

The One Health approach to Mpox control exemplifies a holistic strategy by integrating human health, animal health, and environmental

Table 1
Overview of ongoing vaccine clinical trials: Interventions, phases, and key study details.

Study Title	NCT Number	Interventions	Phases	Start Date
Open-label, Multicenter Immunogenicity and Safety Study of MVA-BN Vaccine in Children From 2 Years to Less Than 12 Years of Age Compared to Adults for the Prevention of Smallpox, Mpox, and Related Orthopoxvirus Infections [92]	NCT06549530	DRUG: MVA-BN	PHASE2	16-10-2024
A Study to Investigate The Safety, Tolerability, And Immune Response of a Range of Doses of mRNA-1769 Compared With Placebo in Healthy Participants From ≥ 18 Years of Age to <50 Years of Age [93]	NCT05995275	BIOLOGICAL: mRNA-1769|OTHER: Placebo	PHASE1| PHASE2	15-08-2023
Smallpox Vaccine for Mpox Post-Exposure Prophylaxis: A Cluster RCT [91]	NCT05745987	DRUG: Bavarian Nordic smallpox vaccine|DRUG: Typhoid VI Polysaccharide Vaccine Injectable Solution	PHASE4	01-09-2024
Efficacy/Effectiveness, Safety, and Immunogenicity of LC16m8 Mpox Vaccine in Colombia [94]	NCT06223919	BIOLOGICAL: LC16m8	PHASE3	16-12-2023
A Clinical Study Investigating the Safety and Immune Responses After Immunization With Investigational Monkeypox Vaccines [95]	NCT05988203	BIOLOGICAL: BNT166a	PHASE1	21-09-2023
A Phase 2 Randomized Multisite Trial to Inform Public Health Strategies Involving the Use of MVA-BN Vaccine for Mpox [96]	NCT05740982	BIOLOGICAL: JYNNEOS	PHASE2	22-03-2023
JYNNEOS Smallpox Vaccine in Adult Healthcare Personnel at Risk for Mpox in the Democratic Republic of the Congo [97]	NCT02977715	BIOLOGICAL: JYNNEOS (Liquid Formulation)| BIOLOGICAL: JYNNEOS (Lyophilized Formulation)	PHASE3	23-02-2017

science to address the complexities of zoonotic diseases. Effective management at the human-animal interface is critical in preventing the spillover of Mpox from wildlife to human populations. This involves rigorous monitoring of wildlife health, controlling the trade of wild animals, and implementing educational programs to raise awareness about the risks associated with wildlife contact. Such measures help mitigate the initial transmission of zoonotic diseases and are fundamental to contain potential outbreaks [17,59]. Environmental changes significantly influence the emergence and spread of Mpox. Deforestation and urbanisation disrupt natural habitats, increasing human-wildlife interactions and the potential for disease transmission. Climate change further exacerbates these risks by altering the distribution and behaviour of wildlife hosts. Recognising these environmental drivers is crucial for developing preemptive strategies considering ecological health as part of disease prevention efforts [28].

The collaboration between human and veterinary health sectors is a cornerstone of the One Health approach. This synergy facilitates the sharing of knowledge and resources, which is essential for the effective surveillance and control of zoonotic diseases. Veterinary experts contribute significantly to our understanding of disease dynamics in animal reservoirs, which is critical for informing public health responses and developing targeted interventions to prevent human infections [19]. Implementing the One Health approach faces challenges such as resource limitations, coordination between diverse sectors, and maintaining sustained funding for interdisciplinary projects. Overcoming these challenges requires robust policy frameworks, dedicated funding, and ongoing collaboration among professionals. Future strategies should also emphasise building capacities in regions most vulnerable to zoonotic diseases, ensuring global health security against Mpox and other emerging infectious diseases [103].

12. Future perspectives

Research should aim to deepen understanding of Mpox transmission dynamics and improve diagnostic, therapeutic, and preventive measures. This includes developing antiviral agents with high efficacy and low toxicity and formulating vaccines that can be effectively deployed during outbreaks [104]. Preparedness strategies must be robust, involving contingency planning, simulation exercises, and stockpiling necessary medical supplies, including vaccines and antiviral medications. Strengthening health care systems to respond to outbreaks effectively with rapid deployment capabilities is essential. As demonstrated by the approaches discussed by Taylor et al. integrating advanced predictive modelling into public health strategies can help authorities anticipate outbreak patterns and optimise response strategies [72].

Practical global cooperation is critical to the surveillance and control of Mpox. This involves sharing real-time data among countries, standardising surveillance methods, and harmonising response strategies to manage outbreaks more efficiently. These strategic areas highlight the necessity of a multidisciplinary approach to manage the Mpox virus effectively. Enhanced research efforts, robust preparedness plans, and strengthened global cooperation will be central to controlling the spread of Mpox and reducing its impact on public health worldwide.

CRediT authorship contribution statement

Parminder Singh: Writing – original draft, Conceptualization. **Sathvik Belagodu Sridhar:** Writing – review & editing. **Javedh Shareef:** Writing – review & editing. **Sirajunisa Talath:** Writing – review & editing. **Priyanka Mohapatra:** Writing – review & editing, Writing – original draft. **Mahalaqua Nazli Khatib:** Writing – review & editing, Writing – original draft. **Suhas Ballal:** Writing – review & editing. **Mandeep Kaur:** Writing – review & editing. **Deepak Nathiya:** Writing – review & editing. **Shilpa Sharma:** Writing – review & editing. **G.V. Siva Prasad:** Writing – review & editing. **Aashna Sinha:** Writing – review & editing. **Amit Varma:** Writing – review & editing. **Ganesh Bushi:** Writing – review & editing. **Abhay M. Gaidhane:** Writing – review & editing. **Prakasini Satapathy:** Writing – review & editing. **Muhammed Shabil:** Writing – review & editing. **Renu Sah:** Writing – review & editing. **Jaffar A. Al-Tawfiq:** Writing – review & editing. **Ranjit Sah:** Writing – review & editing, Conceptualization. **Alfonso J. Rodriguez-Morales:** Writing – review & editing.

Declaration of competing interest

All Authors Declare No Conflict of Interest.

References

[1] Sah R, Apostolopoulos V, Mehta R, Rohilla R, Sah S, Mohanty A, et al. Mpox strikes once more in 2024: declared again as a public health emergency of international concern. Trav Med Infect Dis 2024:102753.
[2] Amer F, Khalil HES, Elahmady M, ElBadawy NE, Zahran WA, Abdelnasser M, et al. Mpox: risks and approaches to prevention. J Infect Public Health 2023;16(6):901–10.
[3] Sulaiman SK, Isma'il Tsiga-Ahmed F, Musa MS, Makama BT, Sulaiman AK, Abdulaziz TB. Global prevalence and correlates of mpox vaccine acceptance and uptake: a systematic review and meta-analysis. Commun Med 2024;4(1):136.
[4] Xiridou M, Miura F, Adam P, Op de Coul E, de Wit J, Wallinga J. The fading of the mpox outbreak among men who have sex with men: a mathematical modelling study. J Infect Dis 2024;230(1):e121–30.

[5] Chaturvedi M, Rodiah I, Kretzschmar M, Scholz S, Lange B, Karch A, et al. Estimating the relative importance of epidemiological and behavioural parameters for epidemic mpox transmission: a modelling study. BMC Med 2024;22(1):297.

[6] Bonilla-Aldana DK, Bonilla-Aldana JL, Ulloque-Badaracco JR, Al-Kassab-Córdova A, Hernandez-Bustamante EA, Alarcon-Braga EA, et al. Mpox infection in animals: a systematic review and meta-analysis. J Infect Public Health 2024;17(7):102431.

[7] Parker E, Omah IF, Varilly P, Magee A, Ayinla AO, Sijuwola AE, et al. Genomic epidemiology uncovers the timing and origin of the emergence of mpox in humans. medRxiv [Preprint] 2024. https://doi.org/10.1101/2024.06.18.24309104. Jun 19:2024.06.18.24309104, PMID: 38947052; PMCID: PMC11213064, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11213064/.

[8] Rousseau A, Ferrier A, Stabler S, Vuotto F, Massip E, Ouafi M, et al. Absence of association between persistent skin lesion and virological replication in severe disseminated monkeypox infection in solid organ transplant recipient. Infect Dis Now 2023;53(6):104749.

[9] Andrei G, Snoeck R. Differences in pathogenicity among the mpox virus clades: impact on drug discovery and vaccine development. Trends Pharmacol Sci 2023;44(10):719–39.

[10] Lim SY, Yim HS, Ahn EJ, Chang E, Yoon J, Suh JH, et al. Severe mpox requiring colostomy in a patient with advanced HIV disease: a case report and literature review. J Infect Chemother 2024. https://pubmed.ncbi.nlm.nih.gov/38936771/.

[11] Mariotti S, Venturi G, Chiantore MV, Teloni R, De Santis R, Amendola A, et al. Antibodies induced by smallpox vaccination after at least 45 Years cross-react with and in vitro neutralize mpox virus: a role for polyclonal B cell activation? Viruses 2024;16(4).

[12] Bunse T, Ziel A, Hagen P, Rigopoulos G, Yasar U, Inan H, et al. Analytical and clinical evaluation of a novel real-time PCR-based detection kit for Mpox virus. Med Microbiol Immunol 2024;213(1):18.

[13] De Pace V, Bruzzone B, Ricucci V, Domnich A, Guarona G, Garzillo G, et al. Molecular diagnosis of human monkeypox virus during 2022-23 outbreak: preliminary evaluation of novel real-time qualitative PCR assays. Microorganisms 2024;12(4).

[14] Aden TA, Blevins P, York SW, Rager S, Balachandran D, Hutson CL, et al. Rapid diagnostic testing for response to the monkeypox outbreak - laboratory response network, United States, may 17-june 30, 2022. MMWR Morb Mortal Wkly Rep 2022;71(28):904–7.

[15] Ouyang ML, Marusinec R, Bayard PJ, Edmunds M, Johnson M, Lai S, et al. Epidemiology of mpox cases, and tecovirimat and JYNNEOS utilization, alameda county, California, june-october 2022. J Publ Health Manag Pract 2024;30(5):744–52.

[16] Weidenthaler H, Vidojkovic S, Martin BK, De Moerlooze L. Real-world safety data for MVA-BN: Increased frequency of syncope following intradermal administration for immunization against mpox disease. Vaccine 2024;42(22):126024. https://doi.org/10.1016/j.vaccine.2024.05.072.

[17] Anglemyer A, Moore TH, Parker L, Chambers T, Grady A, Chiu K, et al. Digital contact tracing technologies in epidemics: a rapid review. Cochrane Database Syst Rev 2020;8(8):CD013699.

[18] Morgan CN, Wendling NM, Baird N, Kling C, Lopez L, Navarra T, et al. One health investigation into mpox and pets, United States. Emerg Infect Dis 2024;30(10).

[19] Sikakulya FK, Mulisya O, Munyambalu DK, Bunduki GK. Ebola in the eastern democratic republic of Congo: one health approach to infectious disease control. One Health 2020;9:100117.

[20] Zinnah MA, Uddin MB, Hasan T, Das S, Khatun F, Hasan MH, et al. The Re-emergence of mpox: old illness, modern challenges. Biomedicines 2024;12(7).

[21] Clinical and epidemiological characteristics of the 2022 mpox outbreak in Spain (CEME-22 study). In: Ramírez-Olivencia G, Velasco Arribas M, Vera García M, Casabona J, Martínez M, Membrillo De Novales F, editors. Open forum infectious diseases. Oxford University Press US; 2024.

[22] Adepoju P. African mpox surges show lack of vaccine access. Lancet 2024;404(10447):18.

[23] Back S, Knox B, Coakley C, Deltour N, Jacquot E, Raad H, et al. Effectiveness and safety of the MVA-BN vaccine against mpox in at-risk individuals in the United States (USMVAc). Vaccines 2024;12(6).

[24] Mercy K, Tibebu B, Fallah M, Faria NR, Ndembi N, Tebeje YK. Mpox continues to spread in Africa and threatens global health security. Nat Med 2024;30(5):1225–6.

[25] WHO. Multi-country outbreak of mpox. 2024.

[26] WHO. Mpox – african region (access date - 23/08/2024) [Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON528; 2024.

[27] Hadfield J, Megill C, Bell SM, Huddleston J, Potter B, Callender C, et al. Nextstrain: real-time tracking of pathogen evolution. Bioinformatics 2018;34(23):4121–3.

[28] Bleichrodt A, Luo R, Kirpich A, Chowell G. Evaluating the forecasting performance of ensemble sub-epidemic frameworks and other time series models for the 2022-2023 mpox epidemic. R Soc Open Sci 2024;11(7):240248.

[29] Yang S, Xia C, Zhang Y, Shen Y, Xia C, Lu Y, et al. Clinical features and viral load variations of Mpox: a retrospective study in Chongqing, China. BMC Infect Dis 2024;24(1):641.

[30] Araf Y, Nipa JF, Naher S, Maliha ST, Rahman H, Arafat KI, et al. Insights into the transmission, host range, genomics, vaccination, and current epidemiology of the monkeypox virus. Vet Med Int 2024;2024(1):8839830.

[31] Ortiz-Martínez Y, Montalvo-Campana M, Saul Z, Gopalratnam K, Wolff AJ, Rodríguez-Morales AJ. Respiratory manifestations and complications of monkeypox. Int J Mycobacteriol 2023;12(3):367–8.

[32] Djuicy DD, Omah IF, Parker E, Tomkins-Tinch CH, Otieno JR, Yifomnjou MHM, et al. Molecular epidemiology of recurrent zoonotic transmission of mpox virus in West Africa. medRxiv [Preprint] 2024. https://doi.org/10.1101/2024.06.18.24309115. Jun 19:2024.06.18.24309115, PMID: 38947021; PMCID: PMC11213044.

[33] O'Neil MJ, Archer R, Danza P, Fisher R, Bagwell DA, Younis I, et al. Successful distribution of tecovirimat during the peak of the mpox outbreak - Los Angeles county, June 2022-january 2023. MMWR Morb Mortal Wkly Rep 2024;73(24):546–50.

[34] Ren R, Li C, Bai W, Wang Y, Li D, Ding F, et al. The epidemiological characteristics of mpox cases - China, 2023. China CDC Wkly 2024;6(26):619–23.

[35] Schwartz DA. High rates of miscarriage and stillbirth among pregnant women with clade I mpox (monkeypox) are confirmed during 2023-2024 DR Congo outbreak in South kivu province. Viruses 2024;16(7).

[36] Calabria de Araujo J, Carvalho APA, Leal CD, Natividade M, Borin M, Guerra A, et al. Detection of multiple human viruses, including mpox, using a wastewater surveillance approach in Brazil. Pathogens 2024;13(7).

[37] Gan G, Janhavi A, Tong G, Lim JT, Dickens BL. The need for pre-emptive control strategies for mpox in Asia and Oceania. Infect Dis Model 2024;9(1):214–23.

[38] Sharpe JD, Charniga K, Byrd KM, Stefanos R, Lewis L, Watson J, et al. Possible exposures among mpox patients without reported male-to-male sexual contact - six U.S. Jurisdictions, november 1-december 14, 2022. MMWR Morb Mortal Wkly Rep 2023;72(35):944–8.

[39] Biesty CP, Hemingway C, Woolgar J, Taylor K, Lawton MD, Waheed MW, et al. Community led health promotion to counter stigma and increase trust amongst priority populations: lessons from the 2022-2023 UK mpox outbreak. BMC Publ Health 2024;24(1):1638.

[40] Karmarkar EN, Cannon CA, Golden MR, Thibault CS, Zinsli K, Kim J, et al. The sexual health clinic role in vaccine and treatment access during the 2022 mpox outbreak in king county. Washington: Sex Transm Dis; 2024.

[41] Qiao H, Paansri P, Escobar LE. Global Mpox spread due to increased air travel. Geospat Health 2024;19(1).

[42] Baraniuk C. Mpox: two years on. BMJ 2024;386:q1554.

[43] Boisson-Walsh A. Escalating mpox epidemic in DR Congo. Lancet Infect Dis 2024;24(8):e487.

[44] WHO. Surveillance, case investigation and contact tracing for mpox (monkeypox): interim guidance, 20 March 2024 [Available from: www.who.int/publications/i/item/WHO-MPX-Surveillance-2024.1. [Accessed 17 September 2024].

[45] WHO. Standing recommendations for mpox issued by the director-general of the world health organization (WHO) in accordance with the international health Regulations. IHR) 2023 [Available from: www.who.int/publications/m/item/standing-recommendations-for-mpox-issued-by-the-director-general-of-the-world-health-organization-(who)-in-accordance-with-the-international-health-regulations-(2005)-(ihr; 2005 (accessed Sep 17, 2024).

[46] Chika-Igwenyi NM, Unigwe US, Ajayi NA, Onwe OE, Ewa RL, Ojide CK, et al. Atypical mpox in a Nigerian tertiary health facility. J Infect Dis 2024;229(Supplement_2):S181–7.

[47] Chakravarty N, Hemani D, Paravastu R, Ahmad Z, Palani SN, Arumugaswami V, et al. Mpox Virus and its ocular surface manifestations. Ocul Surf 2024;34:108–21.

[48] Hosen MI, Mia ME, Islam MN, Khatun MUS, Emon TH, Hossain MA, et al. In-silico approach to characterize the structure and function of a hypothetical protein of Monkeypox virus exploring Chordopox-A20R domain-containing protein activity. Antivir Ther 2024;29(3):13596535241255199.

[49] Peng Q, Xie Y, Kuai L, Wang H, Qi J, Gao GF, et al. Structure of monkeypox virus DNA polymerase holoenzyme. Science 2023;379(6627):100–5.

[50] Zhang W, Liu Y, Yang M, Yang J, Shao Z, Gao Y, et al. Structural and functional insights into the helicase protein E5 of Mpox virus. Cell Discov 2024;10(1):67.

[51] Eaglesham JB, McCarty KL, Kranzusch PJ. Structures of diverse poxin cGAMP nucleases reveal a widespread role for cGAS-STING evasion in host–pathogen conflict. Elife 2020;9:e59753.

[52] Duchoslav V, Boura E. Structure of monkeypox virus poxin: implications for drug design. Arch Virol 2023;168(7):192.

[53] Jiang H, Li J, Jian Y, Yang T, Zhang J, Li J. Expression, purification, and crystal structure of mpox virus A41 protein. Protein Expr Purif 2024;219:106480.

[54] Lum F-M, Torres-Ruesta A, Tay MZ, Lin RTP, Lye DC, Rénia L, et al. Monkeypox: disease epidemiology, host immunity and clinical interventions. Nat Rev Immunol 2022;22(10):597–613.

[55] Ghosh N, Chacko L, Vallamkondu J, Banerjee T, Sarkar C, Singh B, et al. Clinical strategies and therapeutics for human monkeypox virus: a revised perspective on recent outbreaks. Viruses [Internet] 2023;15(7).

[56] Lu J, Xing H, Wang C, Tang M, Wu C, Ye F, et al. Mpox (formerly monkeypox): pathogenesis, prevention, and treatment. Signal Transduct Targeted Ther 2023;8(1):458.

[57] Chakraborty C, Bhattacharya M, Dhama K, Lee SS. Evaluation of differentially expressed genes during replication using gene expression landscape of monkeypox-infected MK2 cells: a bioinformatics and systems biology approach to understanding the genomic pattern of viral replication. J Infect Public Health 2023;16(3):399–409.

[58] Kannan SR, Sachdev S, Reddy AS, Kandasamy SL, Byrareddy SN, Lorson CL, et al. Mutations in the monkeypox virus replication complex: potential contributing factors to the 2022 outbreak. J Autoimmun 2022;133:102928.

[59] Alkhalil A, Strand S, Mucker E, Huggins JW, Jahrling PB, Ibrahim SM. Inhibition of monkeypox virus replication by RNA interference. Virol J 2009;6:188.

[60] Williams J, Bonner J, Kibler K, Jacobs BL. Type I interferon: monkeypox/mpox viruses achilles heel? Adv Exp Med Biol 2024;1451:125–37.

[61] Bruno G, Buccoliero GB. Antivirals against monkeypox (mpox) in humans: an updated narrative review. Life [Internet] 2023;13(10).

[62] Brister JR, Ako-adjei D, Bao Y, Blinkova O. NCBI viral genomes resource. Nucleic Acids Res 2015;43(D1):D571–7.

[63] Izadi M, Mirzaei F, Bagherzadeh MA, Ghiabi S, Khalifeh A. Discovering conserved epitopes of Monkeypox: novel immunoinformatic and machine learning approaches. Heliyon 2024;10(3):e24972.

[64] Tamura K, Stecher G, Kumar S. MEGA11: molecular evolutionary genetics analysis version 11. Mol Biol Evol 2021;38(7):3022–7.

[65] Felsenstein J. Confidence limits on phylogenies: an approach using the bootstrap. Evolution 1985;39(4):783–91.

[66] Benites-Zapata VA, Ulloque-Badaracco JR, Alarcon-Braga EA, Hernandez-Bustamante EA, Mosquera-Rojas MD, Bonilla-Aldana DK, et al. Clinical features, hospitalisation and deaths associated with monkeypox: a systematic review and meta-analysis. Ann Clin Microbiol Antimicrob 2022;21(1):36.

[67] Farahat RA, Sah R, El-Sakka AA, Benmelouka AY, Kundu M, Labieb F, et al. Human monkeypox disease (MPX). Infez Med. 2022;30(3):372–91.

[68] Chastain DB, Krsak M, Henao-Martinez AF. Sex-based differences in treatment approaches and outcomes among patients with mpox: limitations of real-world data. Int J STD AIDS 2024:9564624241254887.

[69] Hammerschlag Y, MacLeod G, Papadakis G, Adan Sanchez A, Druce J, Taiaroa G, et al. Monkeypox infection presenting as genital rash, Australia, May 2022. Euro Surveill 2022;27(22).

[70] Ortiz-Martínez Y, Rodríguez-Morales AJ, Franco-Paredes C, Chastain DB, Gharamti AA, Vargas Barahona L, et al. Monkeypox - a description of the clinical progression of skin lesions: a case report from Colorado, USA. Ther Adv Infect Dis 2022;9:20499361221117726.

[71] Riser AP, Hanley A, Cima M, Lewis L, Saadeh K, Alarcon J, et al. Epidemiologic and clinical features of mpox-associated deaths - United States, may 10, 2022-march 7, 2023. MMWR Morb Mortal Wkly Rep 2023;72(15):404–10.

[72] Taylor H, Humphreys C, Verlander NQ, Bhattacharya A, Vivancos R, Paranthaman K. Emergency department attendances and inpatient admissions due to mpox infection. England: Sex Transm Infect; 2022. 2024.

[73] Ghias S, Joshi N, Cabaravdic D, Nathan R, Takher J. Mpox-induced proctitis. HCA Healthc J Med 2024;5(2):129–32.

[74] Eser-Karlidag G, Chacon-Cruz E, Cag Y, Martinez-Orozco JA, Gudino-Solorio H, Cruz-Flores RA, et al. Features of Mpox infection: the analysis of the data submitted to the ID-IRI network. New Microbes New Infect 2023;53:101154.

[75] Mansoor A, Mansoor E, Waheed Y, Palma PJ, Chaves C. Update on the M-pox virus and safety measures taken against it globally. J Formos Med Assoc 2024;123(10):1030–6. https://doi.org/10.1016/j.jfma.2023.10.019.

[76] Duarte-Neto AN, Goncalves AM, Eliodoro RHA, Martins WD, Claro IM, Valenca IN, et al. Main autopsy findings of visceral involvement by fatal mpox in patients with AIDS: necrotising nodular pneumonia, nodular ulcerative colitis, and diffuse vasculopathy. Lancet Infect Dis 2023;23(11):1218–22.

[77] Croasdale CR, Weinlander E, Boyce TG. Mpox Keratitis: a case report and review. Cornea 2024;43(10):1319–31. https://doi.org/10.1097/ICO.0000000000003614.

[78] Saro-Buendia M, Palacios-Diaz RD, Suarez-Urquiza P, Mansilla-Polo M, Bancalari-Diaz C, Cabrera-Guijo J, et al. Mpox pharyngitis. Indian J Otolaryngol Head Neck Surg 2024;76(3):2902–5.

[79] Fattouh R, Boissinot K, Jeong E, Mendlowitz AB, Sjaarda CP, Wong H, et al. Evaluation of 5 polymerase chain reaction assays for the detection of mpox virus. J Infect Dis 2024;229(Supplement_2):S156–62.

[80] Zhou Y, Chen Z. Mpox: a review of laboratory detection techniques. Arch Virol 2023;168(8):221.

[81] Khan I, S M, Dixit T, Shinkre R, Ravindran S, Bandyopadhyay S. Differential diagnosis, prevention measures, and therapeutic interventions for enhanced monkeypox (mpox) care. Cureus 2024;16(5):e60724.

[82] Bourner J, Garcia-Gallo E, Mbrenga F, Boum 2nd Y, Nakoune E, Paterson A, et al. Challenges in clinical diagnosis of Clade I Mpox: highlighting the need for enhanced diagnostic approaches. PLoS Neglected Trop Dis 2024;18(6):e0012087.

[83] Berhanu A, Prigge JT, Silvera PM, Honeychurch KM, Hruby DE, Grosenbach DW. Treatment with the smallpox antiviral tecovirimat (ST-246) alone or in combination with ACAM2000 vaccination is effective as a postsymptomatic therapy for monkeypox virus infection. Antimicrob Agents Chemother 2015;59(7):4296–300.

[84] Sbrana E, Jordan R, Hruby DE, Mateo RI, Xiao S-Y, Siirin M, et al. Efficacy of the antipoxvirus compound ST-246 for treatment of severe orthopoxvirus infection. Am J Trop Med Hyg 2007;76(4):768–73.

[85] Jordan R, Goff A, Frimm A, Corrado ML, Hensley LE, Byrd CM, et al. ST-246 antiviral efficacy in a nonhuman primate monkeypox model: determination of the minimal effective dose and human dose justification. Antimicrob Agents Chemother 2009;53(5):1817–22.

[86] Sudarmaji N, Kifli N, Hermansyah A, Yeoh SF, Goh B-H, Ming LC. Prevention and treatment of monkeypox: a systematic review of preclinical studies. Viruses 2022;14(11):2496.

[87] Lovett S, Griffith J, Lehnertz N, Fox T, Siwek G, Barnes AMT, et al. Ocular mpox in a breastfeeding healthcare provider. Open Forum Infect Dis 2024;11(6):ofae290.

[88] Paparini S, Whelan I, Mwendera C, Hayes R, Maatouk I, Lewis R, et al. Prevention of sexual transmission of mpox: a systematic review and qualitative evidence synthesis of approaches. Inf Disp 2024;56(8):589–605.

[89] Sah R, Abdelaal A, Asija A, Basnyat S, Sedhai YR, Ghimire S, et al. Monkeypox virus containment: the application of ring vaccination and possible challenges. J Trav Med 2022;29(6).

[90] Abdelaal A, Reda A, Lashin BI, Katamesh BE, Brakat AM, Al-Manaseer BM, et al. Preventing the next pandemic: is live vaccine efficacious against monkeypox, or is there a need for killed virus and mRNA vaccines? Vaccines 2022;10(9).

[91] Smallpox vaccine for mpox post-exposure prophylaxis: a cluster rct (smart). ClinicalTrials.gov identifier: nct05745987. Updated May 22, 2024, https://clinicaltrials.gov/study/NCT05745987. [Accessed 20 August 2024].

[92] Open-label. Multicenter immunogenicity and safety study of MVA-BN vaccine in children from 2 Years to less than 12 Years of age compared to adults for the prevention of smallpox, mpox, and related orthopoxvirus Infections. ClinicalTrials.gov identifier: nct06549530 [Available from: https://clinicaltrials.gov/study/NCT06549530. [Accessed 20 August 2024].

[93] A study to investigate the safety, tolerability, and immune response of a range of doses of mRNA-1769 compared with placebo in healthy participants from ≥18 Years of age to <50 Years of age. ClinicalTrials.gov identifier: nct05995275. https://clinicaltrials.gov/study/NCT05995275. [Accessed 20 August 2024].

[94] Efficacy/effectiveness, safety, and immunogenicity of LC16m8 mpox vaccine in Colombia.ClinicalTrials.gov identifier: nct06223919. Updated August 16, 2024, https://clinicaltrials.gov/study/NCT06223919. [Accessed 20 August 2024].

[95] A clinical study investigating the safety and immune responses after immunization with investigational monkeypox vaccines. ClinicalTrials.gov identifier: nct05988203. https://clinicaltrials.gov/study/NCT05988203. [Accessed 20 August 2024].

[96] A phase 2 randomized multisite trial to inform public health strategies involving the use of MVA-BN vaccine for mpox. ClinicalTrials.gov identifier: nct05740982. Updated August 24, 2024, https://clinicaltrials.gov/study/NCT05740982. [Accessed 20 August 2024].

[97] JYNNEOS smallpox vaccine in adult healthcare personnel at risk for mpox in the democratic republic of the Congo. ClinicalTrials.gov identifier: nct02977715. Updated, https://clinicaltrials.gov/study/NCT02977715. [Accessed 20 August 2024].

[98] Christodoulidou MM, Mabbott NA. Efficacy of smallpox vaccines against Mpox infections in humans. Immunother Adv 2023;3(1):ltad020.

[99] Choudhary OP, Priyanka Fahrni ML, Saied AA, Chopra H. Ring vaccination for monkeypox containment: strategic implementation and challenges. Int J Surg 2022;105:106873.

[100] Koppe U, Jansen K, Schmidt AJ, Weber C, Schulze H, Kulis-Horn RK, et al. Clinically inapparent mpox virus (MPXV) infections among clients of three anonymous Community Based Voluntary Counselling and Testing centres in Berlin, Germany, 2022-2023. BMC Infect Dis 2024;24(1):613.

[101] da Silva K, Granzotti RBG, Cesar C, Barretto RBS, Santos NM, Cruz PJA, et al. Emerging challenges of Mpox transmission: an in-depth scoping review and evidence mapping on breastfeeding practices in South America. Pediatr Infect Dis J 2024;43(10):e341–6. https://doi.org/10.1097/INF.0000000000004432.

[102] Forouzan P., Raffi J., Doan L.T., Min M.S. Reactive lobular panniculitis in the setting of Mpox (Monkeypox) infection. Am J Dermatopathol. doi:10.1097/DAD.0000000000002795. Published online July 16, 2024.

[103] Singh S, Sharma P, Pal N, Sarma DK, Tiwari R, Kumar M. Holistic one health surveillance framework: synergizing environmental, animal, and human determinants for enhanced infectious disease management. ACS Infect Dis 2024;10(3):808–26.

[104] Li E, Gong Q, Zhang J, Guo X, Xie W, Chen D, et al. An mpox quadrivalent mRNA vaccine protects mice from lethal vaccinia virus challenge. Antivir Res 2024:105974.