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REVIEW ARTICLE

Origin, Epidemiology, Transmission, Clinical Symptoms, and Future Perspectives on Mpox Virus (MPXV): A Narrative Review

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Abstract

Monkeypox (MPX) has long been a problem for many nations, particularly African nations, with recurring outbreaks in specific areas. The pathogenicity-dependent genetic variations, the mode of transmission, the lifestyle of the population, the growth in the number of viable hosts, alterations to their habitats, and the vaccination profile of humans are all directly related to the rate at which MPX spreads. Despite having a minimal potential for global transmission, it should be remembered that in today's globalized society, an unexpected breakout is always possible. One of the constant dangers to humanity is the advent of new diseases. New infections have the chance to develop as a result of ongoing environmental and human intervention. Human activity, international travel, and business frequently contribute to the spread of disease. The dynamics of mpox transmission and the progression of the disease are poorly understood. Controlling such outbreaks is mostly the responsibility of central organizations like the World Health Organization. However, maintaining good personal cleanliness, avoiding contact with used objects, and avoiding animal feces are the best ways to be safe. In 2022, the endemic disease status of MPX was revised to worldwide outbreak. This is the main cause for the condition's prevalence outside of Africa: it was deemed a worldwide health emergency, independent of travel restrictions. Clinical indications that are typical and serve as an indicator for the initial stage of diagnosis include fever, headache and muscle discomfort, enlarged lymph nodes, and skin rashes in certain body locations. The most popular and reliable diagnostic techniques are clinical symptoms and laboratory tests such as real-time PCR (RT-PCR) or traditional polymerase chain reaction (PCR). For symptomatic treatment, antiviral medications such as tecovirimat, cidofovir and brincidofovir are utilized. Although there isn't a vaccination specifically for MPXV, the smallpox vaccines that are now on the market increase the immunization rate. A greater understanding of MPXV transmission mechanisms by the general public could enable early identification of the spread of new cases to other populations. [*Journal of Current and Advance Medical Research, January 2024;11(1):41-49*]

Keywords: Monkeypox; Genome; Transmission; Tecovirimat; Prevention

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Introduction

Monkeypox (MPX) is a zoonotic viral disease caused by the Monkeypox virus (MPXV), a double-stranded DNA virus. According to the most recent International Committee on Taxonomy of Viruses (ICTV) update from August 2022,[1] monkeypox (MPX) is an enveloped DNA virus and is a member of the Poxviridae family of the genus Orthopoxvirus. Its genome is between 180 and 220 kilobase pairs (kb) in size and encodes about 200 genes. The size of the virions is around 250 nm × 220 nm. The viral core is released into the cytoplasm by a low-pH-dependent macro-pinocytotic uptake, which permits viral entry into the cell. The viral core is where early gene expression and virus uncoating start[2]. This leads to the intermediate and late stages of gene expression, which is followed by DNA replication. Mature viral particles are created by the assembly of structural proteins, viral enzymes and DNA molecules[3].

Its primary host is unknown[4,5]. Initially identified in a monkey during vaccination research in 1958, it has been documented in a number of reservoirs, particularly in rodents and other small mammal species[6,7]. However, the disease was not termed MPX until 1970, when the first human case, a Congolese child was documented[8,9]. All of the earliest instances which were documented, were endemic and registered in African nations; nevertheless, human-to-human transmission became serious between 1996 and 1997[4,10]. Long-term close contact, respiratory droplets, contaminated personal belongings and direct touch with rash sites are some of the mediators for transmission[11].

Approximately thirty years later, the first MPX case outside Africa, due to virus infection via zoonotic transmission from an infected animal, was recorded in the U.S. The key factors in the disease outbreak were travelling from African countries and animal importation. MPX cases were then periodically reported all across the world. But in 2022, the MPX pandemic spread internationally, and as a result, it was deemed a global health emergency apart from travel-related concerns[12]. The World Health Organization (WHO) recommended substituting the term "mpox" for "monkeypox" on November 28, 2022. "Monkeypox" is being phased out, and both terms will be used for a year[10].

The WHO's "2022 Mpox Outbreak" report, released on January 16, 2023, stated that 110 countries, regions, or territories reported MPX cases. Among them, 103 spoke for the first time[10,13]. As of January 16, 2023, the overall number of confirmed cases was 84,716; the United States had the most cases, with 29,980.

So far, 80 deaths have been documented worldwide; the leading nations are the United States (21), Brazil (14), Peru (12), Nigeria (7), Mexico (4) and Spain (3) (Fig. Ia). Global cases since the outbreak's beginning reached their greatest value in August 2022; afterward, they steadily dropped and are currently stable. (Figure Ib).

We perform phylogenetic analysis on known MPXV genomes and present a narrative overview of previously available material regarding MPXV in light of the recent rise in mpox cases. We focus on the evolution of MPXV in humans as new cases are discovered.

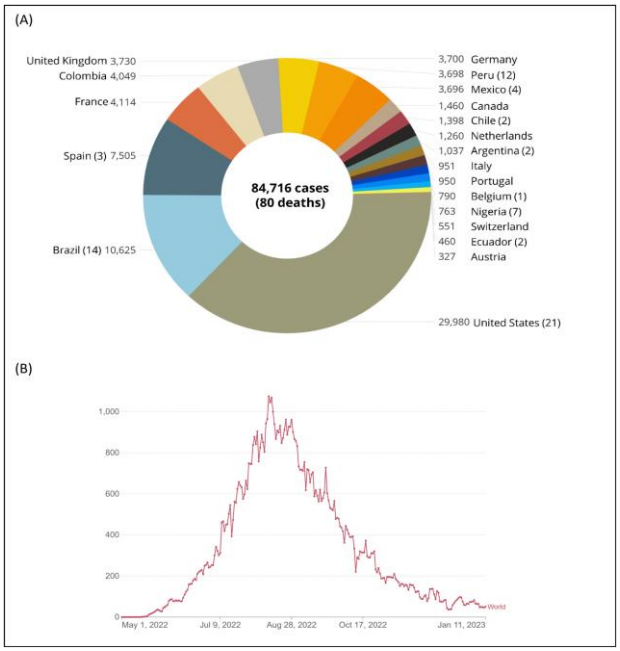

Figure I: The number of confirmed MPX or mpox cases globally. **(a)** The top 20 countries have the highest cases as of 16 January 2023. The death tolls are indicated in parenthesis (the World Health Organization, 2022 Mpox Outbreak[10]) **(b)** Weekly distribution of the global cases from the beginning of the outbreak (OurWorldInData[14]) Note: For the WHO European region, confirmed and probable cases are included within confirmed case counts.

Origin and Classification of MPXV

There are 22 genera and 83 species in the Poxviridae family, which is further divided into two subfamilies: Entomopoxvarinae (4 genera and 31 species) and Chordopoxvirinae (18 genera and 52 species)[1]. There are 12 known members of the genus Orthopoxvirus, which affects both humans

and animals. In addition to MPXV, vaccinia virus (smallpox vaccine virus), Abatino macacapox virus, Akhmeta virus, Camelpox virus, Cowpox virus, Ectromelia virus, Raccoonpox virus, Skunkpox virus, Taterapox virus, and Volepox virus[1], the most well-known member is the variola virus, which causes smallpox.

There are two known viral clades: the Central African (Congo Basin) clade and the West African clade.[15] Viruses from Central Africa are more virulent than those from West Africa[16,17]. Compared to the West African clade (4%), the central African clade is said to be more severe and exhibit a greater death rate (10%)[10,18]. Variabilities in genome organization brought on by deleted gene sections and gene fragmentation in open reading frames are the source of the variations in virulence[11]. Therefore, gathering samples from various regions, people, and clades is essential for figuring out the MPXV's genetic characteristics as well as validating the cases and research facilities[19].

Transmission of MPXV

It is believed that rodents make up the majority of the reservoirs, with humans and monkeys serving as inadvertent hosts[20]. Despite its name, MPXV is not derived from monkeys. There are other ways that MPXV might spread, including from animal to human, animal to animal, and human to human (Fig. II). Direct contact with an infected animal or bodily fluids is the most frequent way that the disease is spread from animal to person[11]. Animal contact has been linked to infections in humans. However, because of rodent infestations in dwellings and the hunting or preparation of bushmeat from other species, it is difficult to pinpoint the precise way in which a human individual was exposed in areas where animal contact occurs often[21]. There have been reports of human-to-human transmission in West Africa and Nigeria[22]. Living in the same house or using the same dishes, close contact, fomites, or coming into direct contact with an infected person's skin sores can all spread the infection[21]. Furthermore, the CDC updated new outbreaks to include potential transmissions such kissing, embracing, and oral, anal, and vaginal sex, which may be linked to genetic alterations that facilitate the MPXV's human-to-human spread[18]. Robust data additionally indicates that the primary mode of MPXV transmission at this time is sexual; this can occur through intimate contact or directly through animal-to-human and human-to-human contact. Sexual transmission, particularly between men who have sex with males, gained significance during the global outbreak of 2022[1].

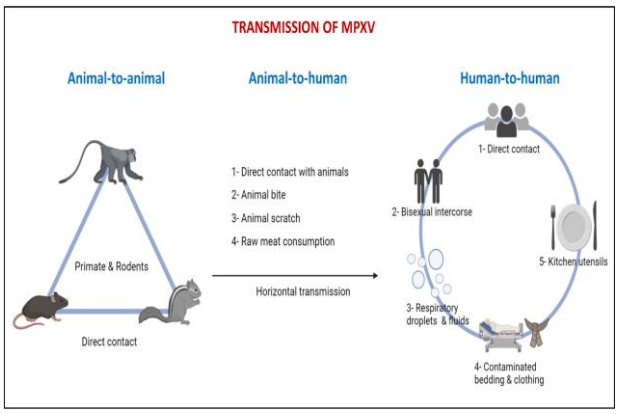

Figure II: The transmission of the MPXV is animal-to-animal, animal-to-human, and human-to-human[11]

Certain symptoms are frequently seen, even though the disease's incidence and severity vary with age and gender. In comparison to earlier clades, the current circulating variant may exhibit presymptomatic transmission, have milder clinical presentations, and be more prevalent among men who have sex with men (MSMs). These factors all point to the possibility that mpox has evolved a unique clinical phenotype that has increased its transmissibility.

Epidemiology

In September 2018, the MPXV was spread from a patient to a healthcare worker in the United Kingdom as a result of tainted bedding[23]. According to Vivancos et al[24], there has been a persistent MPXV infection outbreak in the UK since May 2022. Additionally, visiting Nigeria was a factor in the MPX cases that were found in Singapore and Israel[25]. The West African lineage was the source of the majority of the identified cases in the 2022 outbreak in Europe[26-27]. After two outbreaks of a nonfatal rash disease in captive Singaporean cynomolgus macaques, MPXV was first isolated in Copenhagen, Denmark, in 1958[28]. Similar outbreaks were noted in American and European primate colonies in the ensuing decade[29]. At the time of initial human identification, 282 cases were documented in Zaire between 1980 and 1985. Ninety percent of them were under fifteen, and their ages ranged from one month to 69 years. Vaccinated patients showed no death, whereas unvaccinated cases had an average fatality rate of 11%, with higher rates in children (15%)[30]. (Table I). Previously, vaccinia was used to develop

protection against the MPXV; however, the elimination of smallpox and the ensuing reduction in the vaccination effort prevented the development of immunity against MPX. The underestimation of the dangerous potential of this contagious virus was a result of the paucity of reporting from rural Africa[31]. The fact that MPXV outbreaks have occurred outside of Africa shows how widespread the virus is! Programs those support MPXV surveillance and diagnosis are therefore essential to understanding the infectious disease's shifting epidemiology[32]. MPXV spread to industrialized nations but did not halt in Africa. In July 2021, two MPX cases were recorded in the United States in individuals returning to Texas from Nigeria. On 6th May 2022, a British man's case was reported after his trip to Nigeria. Approximately 1500 cases have been documented in over 43 countries, including North America and Europe, as of June 2022. While the MPXV is prevalent in central and western Africa, there have also been reports of MPX symptoms spreading globally in the industrialized world. All incidences of infection were linked to either animal shipping or travel to Africa. With 29,980 cases and 80 fatalities, the United States is the new outbreak hub. This poses a worldwide risk, which makes it imperative to develop a strategic plan to stop MPXV from spreading like wildfire[33].

Genome Organization and Viral Entry Mechanism of MPXV

The MPXV's double-stranded DNA (dsDNA) genome is approximately 197.2 kb in size and contains more than 190 open reading frames (ORFs), which encode 181 proteins[34,35]. The genome's highly conserved central coding region is flanked by various ends containing inverted terminal repeats. Poxvirus replication and morphogenesis require a minimum of 90 open reading frames (ORFs). Many so-called non-essential ORFs contribute to variances in poxvirus host tropism, immunomodulation, and pathogenicity, and many ORFs have yet to be functionally identified[36]. MPXV virions have an average size of 280 nm to 220 nm and are shaped like barrels or ovals[37]. Poxvirus mature particles have a unique dumbbell-shaped nucleoprotein core that houses a huge genome. The core region of the MPXV genome contains genes that are known to be critical for orthopoxviruses[34,38]. However, unlike other orthopoxvirus genomes, a small number of ORFs are deleted or shortened in the MPXV genome[34,39,40]. The linear genome has covalently closed hairpin ends. The 10 kb inverted terminal repeats (ITR) are found at both ends of the genome (Figure III). Genes are densely packed; intergenic regions greater than 100 bp are unusual. The conserved center section encodes the "housekeeping" genes required for transcription, replication, and virion assembly. The genes encoded in the terminal domains differ between poxviruses, resulting in proteins with simplified disease and host ranges. The first complete MPXV genome of the current MPXV epidemic (isolate name MPXV_U.S._2022_MA001) was released in the GenBank database with an accession ID of ON563414 on May 30, 2022[41]. The Oxford nanopore technologies indicated that MPXV's genome size is 197,205 bp as linear dsDNA. The average size of the MPXV is between 200 and 250 nm. The MPXV replicates in the infected host cell's cytoplasm and consists of a core area with lateral bodies, double-stranded deoxyribonucleic acid (dsDNA), and a lipoprotein envelope. Micropinocytosis, viral endocytosis, and cell membrane fusion all help viral entrance through the nasopharyngeal, oropharyngeal, subcutaneous, intradermal, and intramuscular pathways.

MPXV replication at the inoculation triggers inflammatory immune-mediated phagocytosis, which spreads the virus to the blood, lymph nodes, tonsils, bone marrow, spleen, and other organs. MPXV mature virions (MV) and enveloped virions (EV) regulate the release of the MPXV genome and proteins into host cells. Following MPXV mRNA transcription and translation, intracellular mature virions (IMV) containing viral DNA encoding the virus are formed. IMVs wrapped in Golgi apparatus-derived membranes produce intracellular enveloped virions (IEVs), which fuse with the host inner cell membrane to form cell-associated virions (CEVs) before being released into extracellular spaces to form extracellular enveloped virions (EEVs) [42].

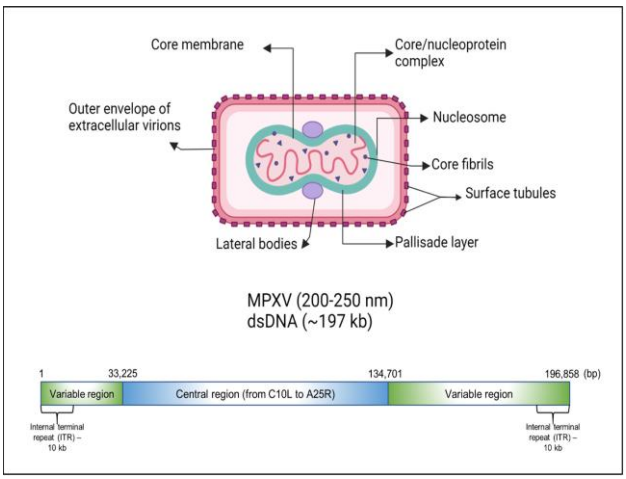

Figure III: The structure of the MPXV and its genome[34,35]

Clinical Symptoms

The most common signs and complications are respiratory distress, sepsis, gastrointestinal and oral ulcers, fever, lymphadenopathy, ocular infection, and skin infection like scarring, cellulitis or other skin lesions[11]. 96% of the cases have rashes, and 69% have flu-like symptoms[18]. Clinical indications that last two to four weeks can appear abruptly and progress slowly[43]. Nonetheless, the severity and course of the MPX disease vary by individual. In December 2016, a four-year-old boy from the Democratic Republic of the Congo was admitted to the hospital on the third day of symptomatic illness with fever, rhinitis, conjunctivitis, cough, one-sided cervical lymphadenitis, and vesiculopapular rashes covering his entire body and face. These symptoms were considered to be measles or chickenpox; but, due to a lack of diagnostic equipment, no tests could be performed on the patient. Supportive therapy began early, although they were ineffective in preventing the symptoms from deteriorating. On the 12th day of admission, the child died, and a blood test for measles was also negative[44]. In Nigeria outbreak of 2017-2018, 122 confirmed MPX cases aged 2 days to 50 years were investigated. All patients experienced vesiculopustular rashes all over their bodies, particularly on their faces, as well as other typical symptoms like fever, pruritus, headache, and lymphadenopathy[45]. Although no studies have been conducted on sexual transmission of MPX, the 2022 outbreak mentions new symptoms and a population via that route[1]. During the 2022 London outbreak, 197 recorded cases were all male, with 196 being gay, bisexual, or having sexual intercourse with another man, according to a study from the London HCID Center. These findings differ significantly from past outbreaks. All individuals exhibited mucocutaneous lesions, particularly in the vaginal and perianal areas. In contrast, rectal pain and penile edema (swelling) were newly and often reported during this outbreak. In the latest outbreaks, lesions were heavily localized in the genitals and perianal regions, whereas in earlier cases, the distribution of lesions concentrated on the trunk, face, leg, head, and arms[43]. In past epidemics, a greater percentage of illnesses were in children, and the majority of the population had received a smallpox vaccination. Children and adults, particularly men, have been affected by recent MPX outbreaks of the West African and Basin clades.

Therapeutic Options and Prevention

The approach to treating an Orthomyxovirus infection is quite similar to that used to prevent and treat mpox[46]. The epidemic in 2022 made clear how urgent it is to stop the spread of mpox because it poses a risk in many nations[47]. The condition is not treated with drugs that are specific to MPXV; there is currently no known treatment for mpox infection, however patients can manage their moderate symptoms and prevent more complications with supportive care[48-49]. Research has shown that people with minor symptoms get better on their own[50–52]. However, smallpox and mpox share a lot of clinical similarities, mpox can be effectively treated with smallpox treatment methods. These include antiviral medications including cidofovir, tecovirimat, and brincidofovir, as well as the vaccinia vaccine and vaccinia immune globulin (VIG)[51]. Furthermore, because the present medications have major side effects and their therapeutic efficacy is yet unknown, the CDC advises using the potential treatment options based on the severity of the illnesses and for serious emergency cases[52]. The FDA has licensed VIG (vaccinia immunoglobulin), a hyperimmune globulin, to lessen the side effects of live vaccines (such ACAM2000)[53]. Although VIG should be used in accordance with the investigational new drug (IND protocol), its effectiveness against smallpox and MPX has not been established. Protective antibodies are seen in the hyperimmune plasma obtained from live vaccine recipients. Antiviral medications are a therapy option for immunocompromised patients, people with complex lesions, pregnant women with mpox, nursing mothers, and children[54]. First-line antiviral medication advised for smallpox treatment is tecovirimat; it prevents the virus's last stages of maturation and escape from infected cells by blocking the viral envelope protein, which stops the virus from spreading. According to CDC guidelines, tecovirimat may be used for compassionate purposes in emergency situations to treat Orthopoxvirus infections, including mpox[55-56]. Commonly prescribed medications for smallpox therapy include cidofovir and its oral counterpart brincidofovir; both work by blocking viral DNA polymerase.

The effectiveness of brincidofovir against Orthopoxvirus infections has been assessed in a number of trials[57]. There has been modest success in evaluating the effects of cidofovir and brincidofovir for mpox in studies[54,57]. Pre-exposure smallpox immunization has been recommended for veterinarians, monkey pox contacts, healthcare workers, researchers, and field investigators in accordance with the CDC's recommended standards[58]. Three smallpox vaccines are currently available in the US national stockpile:

JYNNEOSTM, ACAM2000, and the most recent, Aventis Pasteur Smallpox Vaccine (APSV), which has a 2007 smallpox license and may be used for mpox on an as-needed basis under an investigational new drug (IND) protocol. The modified vaccinia Ankara-Bavarian Nordic is used to make JYNNEOSTM, a third-generation live viral vaccine[59-61]. JYNNEOSTM is an attenuated non-replicating orthopoxvirus that was licensed in 2019. It is currently recommended for adults to avoid smallpox and mpox. Additionally, during the outbreak, ACAM2000, a second-generation vaccination made of live vaccinia virus, is permitted for mpox. These vaccinations can be administered both before and after therapy to either prevent infection and disease or to worsen infection and disease, according to research findings[54,62-63].

Research has shown that antiviral therapy is preferable to immunization for immune-compromised patients, pregnant women, and children under the age of eight. Despite being licensed, these vaccines have caused a number of local and systemic side effects, including fever, headache, weariness, muscle and back discomfort, lymphadenopathy, and more[61–63]. The necessity of upholding suitable social barriers, such as avoiding intimate contact with afflicted individuals and avoiding touch with skin lesions of MPXV-infected individuals, has also been emphasized by researchers[63–65]. Although there is little information regarding its efficacy in treating mpox, vaccine immune globulin intravenous (VIGIV) is a therapy option in cases of severe infection. Therefore, depending on the severity of instances and the patients' immunological status, therapeutic options and vaccine repurposing must be evaluated case-by-case[66] (Figure IV).

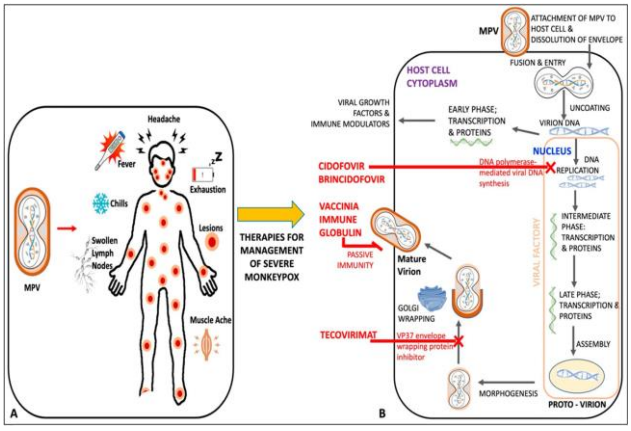

Figure IV: A Symptoms and **B** mechanism of action of mpox antiviral therapy: cidofovir, brincidofovir, vaccinia immune globulin, and tecovirimat[66]

New Variety in the Current Outbreak

A novel lineage B.1, categorized as clade IIb due to its strong ties to clade II, has been found in the current outbreak in 2022[67-68]. The present strain of MPXV in the UK exhibits 48 single changes in its genome when compared to strain sequencing from 2018, despite the fact that the novel B.1 lineage has been linked to strains that were circulating in Nigeria during the 2017 outbreak[69-70]. This indicates a mutation rate that is 6–12 times greater than what was previously thought[67].

The circulating MPXV appears to have originated from the clade sampled in patients from Nigeria, Singapore, Israel, and the UK between 2017 and 2019, according to sequencing by Isidro and colleagues[71]. An open-source project called Next strain, which enables real-time tracking of pathogen evolution, conducted a molecular clock analysis of this virus and revealed a great deal of variation in the descendent lineages of MPXV (A.1, A.2, A.1.1, and B.1)[72]. It was noted that these fast mutations might be caused by a cytosine deaminase known as the apolipoprotein B editing complex (Apolipoprotein B mRNA Editing Catalytic Polypepide-likee3, APOBEC3)[73].

Future Perspective

In order to unravel MPX, it is essential to analyze both present and future examples. For example, nothing is known about the effects of human interaction, animal population, and area on MPX. Furthermore, there are still unanswered problems regarding the identification of possible reservoirs, the impact of season on disease incidence, travel status, and age distribution at MPX infection. In order to lower the incidence of transmission and offer medical assistance, governments, research institutions, and authorized organizations should all agree on early diagnosis indicators. More importantly, they should design various strategies for immunization programs. Therefore, a wide range of studies and additional study are required to stop other potential hazards to public health and global issues.

First, the general population's waning immunity following the termination of smallpox immunization is probably the reason why MPXV transmission has grown over time. Second, a large portion of the infections in the present outbreak are caused by direct contact between young MSMs. As a result, the environment in which the virus is now spreading (high rates of close contact) may increase

the number of onward transmissions per patient. Likewise, there may be varying degrees of variability in the quantity of secondary transmissions per index instance.

These figures will be affected by the number of home contacts, awareness of the disease, and any public health measures used. According to Beer and Rao's 2019 comprehensive assessment of prior epidemics in Central and West Africa, secondary attack rates among household contacts who were not vaccinated against smallpox ranged from 0% to 11.0%[74].

Secondary attack rates among vaccinated household contacts were significantly lower; according to a 1988 study, the secondary attack rate among unprotected household contacts was 9.0%, while the rate for vaccinated contacts was 1.0%. Additionally, Beer and colleagues observed that between 1981 and 2005, the "crude" secondary attack rates rose, most likely as a result of a rise in the population's percentage of unvaccinated people.

Conclusion

There is a paucity of routine illness surveillance in mpox endemic areas. This also entails encouraging financing for the capacity building needed for disease surveillance, research, and testing facilities. However, the control methods are significantly impacted when health bodies such as WHO guidelines and laws are not followed. To stop outbreaks in the future, it is crucial to accelerate the development of vaccines and efficient medications. Additionally, as new plant-derived products may have less adverse effects when used to treat mpox, they could be encouraged and further explored. Social gatherings were made possible by the reduction of sickness rates brought about by new medications and immunizations. However, it must be recognized that these diseases still affect human lives and the decisions will influence how things turn out.

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Conflict of Interest
The authors have no conflicts of interest to disclose

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Data Availability
Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate
Not Applicable

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