Monkeypox: The Re-Emergence of a Neglected Zoonotic Threat

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Abstract

Monkeypox is a zoonotic disease and caused by the monkeypox, an Orthopoxvirus. Since the first case in human was identified in the Democratic Republic of the Congo in 1970, the disease has caused outbreaks and sporadic infections. In July 2022, the World Health Organization declared monkeypox a Public Health Emergency of International Concern. The incubation period of monkeypox in the 2022 outbreak was 7 to 10 days, and symptoms of the disease include fever, myalgia, and a distinctive rash which includes papules that develop into vesicles, pustules, and crusts in the oral, genital, or anal areas and frequently affects the mucosa. Penile edema, rectal discomfort, odynophagia, and cutaneous and anorectal abscesses are among the complications that need medical attention. The majority of individuals' illnesses are self-limiting. Viral DNA positive PCR can be used to make a diagnosis. Antiviral therapy may be helpful for patients with severe symptoms of diseases and those who are at risk of severe illness. The non-replicating modified vaccine Ankara is currently used as a post-exposure prophylactic or pre-exposure prophylactic for high-risk individuals. In Africa's endemic nations, antiviral therapy and vaccinations are still unavailable.

Keywords: Mpox, emerging zoonosis, smallpox, transmission, Vaccination

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Introduction

Monkeypox (Mpox) is a new viral zoonotic illness and the Monkeypox virus (MPXV) is the causative agent of it. This virus belongs to the Family *Poxviridae* (Di Giulio & Eckburg, 2004). Monkeypox viral disease is a potential zoonotic disease with public health inferences due to its transmission from animals to humans and person-person (Bunge et al., 2022). Monkeypox disease was first characterized among monkeys in 1958 (Anil et al., 2024). In succeeding years, outbreaks were reported in captive monkeys in the USA, France and Netherlands (Parker & Buller, 2013). In case of humans, the first incidence of this viral disease was informed in 1970 in the Democratic Republic of the Congo in a young male without vaccination of smallpox at the age of 9 months. It has been estimated that preceding vaccination against smallpox is 85% effective in preventing monkeypox disease (Tripathi et al., 2025). The isolates of the monkeypox virus were divided into two clades based on their clinical and genomic sequencing images. In the Democratic Republic of the Congo (DRC), from 1981 to 2017, monkeypox clade 1 was responsible for many outbreaks with high case fatality rate (Mandja et al., 2019). Since the discovery of monkeypox disease, sporadic outbreaks have sustained in several western and central African countries. It is endemic in these regions but common in rural rainforest regions (Yinka-Ogunleye et al., 2018). In endemic areas, monkeypox virus mostly circulates among animal reservoirs, mainly of rodents (Ullah et al., 2023).

Travel from African nations and the importing of animals were the primary causes of the disease outbreak. The MPX cases were then periodically reported all across the world. However, the MPX outbreak expanded internationally in 2022, and as a result, it was deemed a global health emergency separate from travel-related concerns (Farasani, 2022). In the past, MPX was thought to be less deadly than smallpox symptoms. But as time went on, the MPX virus grew more dangerous and led to an outbreak (Karagoz et al., 2023).

The Source and Taxonomy of Mpox

There are 22 genera and 83 species in the Family Poxviridae which is sub-divided into 2 subfamilies, named as Entomopoxvarinae and

the Chordopoxvirinae families. There are 12 known members of the genus Orthopoxvirus, which affects both humans and animals (Siddell et al., 2023). The 2 recognized viral clades of MPX are the Central African (Congo Basin) and the West African clades (Likos et al., 2005). On comparison basis, Central African viruses are more infectious than West African viruses (Hutson et al., 2010). During the 2003 U.S. outbreak, the Central African lineage of human MPX illness was linked to high rates of morbidity, mortality, person-to-person transmission, and viremia (McCollum & Damon, 2014). Compared to the West African clade, which has a 10% fatality rate, the central African clade is said to be more severe (Lin et al., 2024). Differences in genomic organization caused by gene-fragmentation in open reading frames and deleted gene sections result in variations in virulence (Kaler et al., 2022).

Morphology

Among several poxviruses, the monkeypox virus is the leading and maybe most adaptable virus (Barreto-Vieira & Barth, 2015). They are brick-like, measuring between 220 - 450 nm in length and 140 - 260 nm in width (Jahrling et al., 2007). Therefore, MPXV is large enough to be visible under a microscope, and electron microscopy can be used to resolve its ultrastructure. However, higher resolution provided by electron microscopy is necessary to identify structure and function of the virus (Moss & Damon, 2013). The 4 main parts of the Orthopox virion are the outer membrane, outer lipoprotein envelope, core, and lateral bodies (Figure 1). The central core of the virus contains the core fibrils and double-stranded DNA (dsDNA). The apical surface is a tightly packed layer of rod-shaped components that surround the core. The outer layer encloses the palisade layer, peripheral bodies, and central core. It is composed of several external glomeruli, whereas virions produced by the cellular disruption lack the membrane, spontaneously released virions typically have the external lipoprotein envelope (Malik et al., 2020).

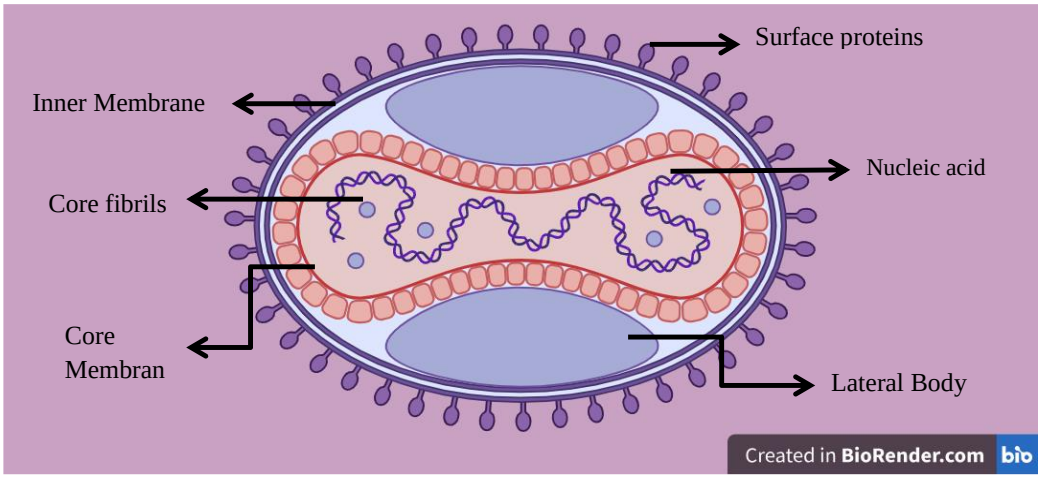

Figure 1: Schematic illustration of monkeypox virus highlighting the structure of monkeypox virus with its surface proteins, membranes, and its internal components which are responsible for replication within host cells.

Genome

The genome of monkeypox is one of the largest viral genomes, consisting of a single, 197 kbp dsDNA molecule (Moss & Damon, 2013). There are a number of brief repetitive sequences at each terminus of the genome and have terminal hairpin loops as well as similar but inverted terminal copies, each about 6 kbp in size. The genome is composed of around 190 non-overlapping open reading frames (above 180 bp long) with 60 or more amino acid deposits. Four of these are in the reversed terminal repeat (Shchelkunov et al., 2002). The guanine and cytosine content of MPX viral DNA is low, and approximately 31.1% (Shchelkunov et al., 2001). The MPXV haplotypes from West Africa (WA) and Central Africa (CA) have been distinguished as distinct genetic lineages (Likos et al., 2005). Numerous OPVs' whole genome sequencing revealed a high degree of variation in the regions located on each end of the genome and a high proportion of commonality in the core genes. The pathogenicity of different OPVs is probably correlated with variable OPV terminal sequences (Tulman et al., 2006) because essential viral functions like virion assembly and replication are usually carried out by fixed OPV genes (Seet et al., 2003). Several terminal genes support innate immunity through their interactions with antigen signaling, distribution, identification, and death (Barry et al., 2004).

Viral Replication Cycle

Poxviruses replicate in the host cell's mitochondrial matrix, in contrast to other DNA viruses. Poxviruses use a refined strategy that includes adhesion, hemi fusion, and core entry at the cell membrane or following the process of endocytosis to enter the cell (Moss, 2016). Poxviruses enter cells in different ways; depending on whether they are extrinsic enveloped virion (EV), which has an outer layer with a specific amino acid composition, or mature virion (MV), which has a simple outer membrane. In EV form, the underlying MV membrane is exposed when the outer EV-specific membrane is shed, and it then joins the cell. Actin polymerization gives EV its long, mobile projections that adhere to the cell surface, making it suited for cell-to-cell transmission (Aljabali et al., 2022)

Once in the cytoplasm, the viruses release packed viral proteins and catalytic components that weaken cell mechanism of defense and encourage the expression of earlier genes. The adult virion is first uncoated after entrance. The primary messenger RNA (mRNA) is then produced by viral DNA-dependent RNA polymerase enzymes. Initial mRNA translation facilitates DNA replication, the 2nd uncoating phase, and the production of intermediate transcriptional regulators. The creation of late mRNAs and their conversion into functional, non-structural entities (enzymes and early transcription factors) follow the translation and transcription of intermediate mRNA. With DNA concatemers produced during the early phases of replication, the translated molecules are bundled into adolescent virions, which develop into internal matured virions (IMVs). Because of their lack of an outer sheath, IMVs are only contagious when they are liberated by cell breakdown. IMV

particles that fail to enclose themselves within the cytoplasmic protein matrix develop a second barrier and transform into cytoplasmic encapsulated virions (IEVs) (Roberts & Smith, 2008).

In order to create cell-associated virions (CEVs), they move to the internal cell membrane using microtubules and fuse with it. This resulted in actin polymerization and the formation of filaments that let CEVs escape the cell (Figure 2). The CEVs that have exited the cell are known as extracellular enveloped virions (EEVs) (Bray & Buller, 2004).

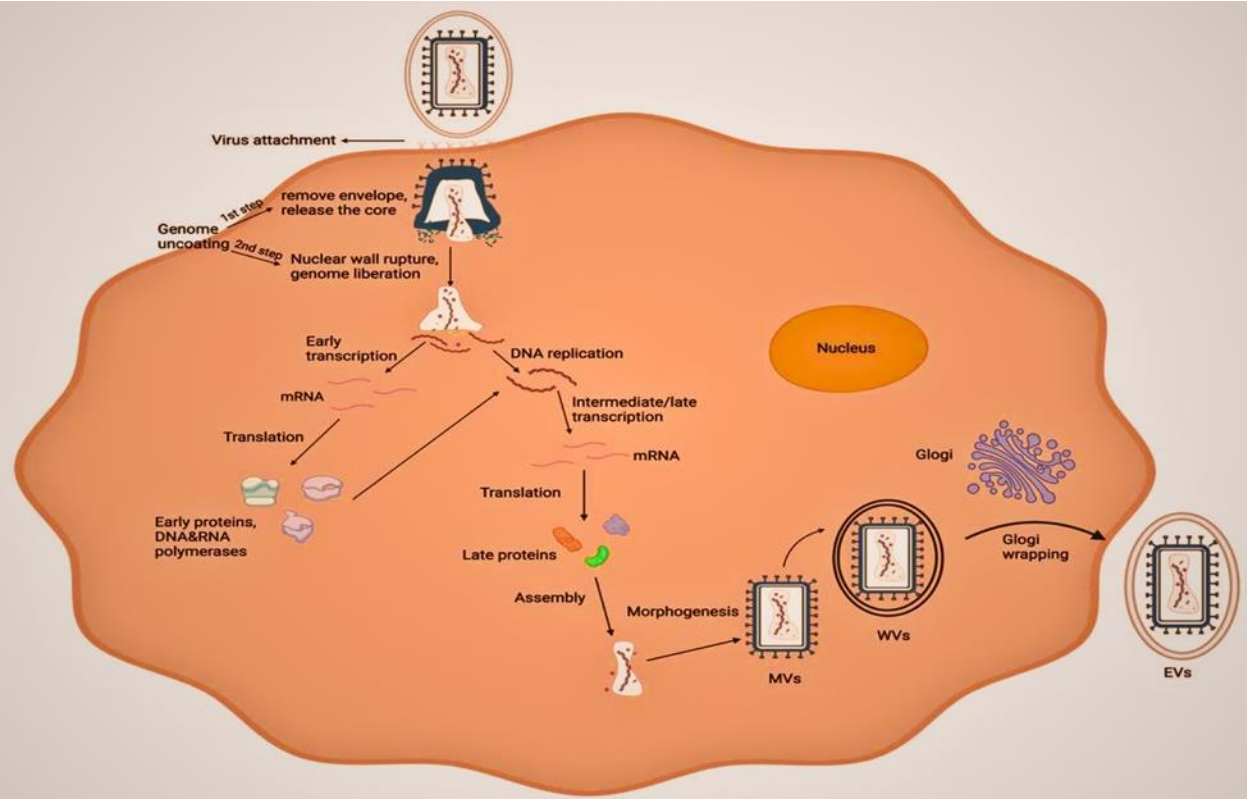

Figure 2: Monkeypox virus replication within the host cell

Transmission

Monkeypox disease transmission is possible because of the contact with bodily fluids, skin lesions, waste products harboring the virus, respiratory droplets from sick animals, and infected fomites. Although there hasn't been much person-to-person transmission in the past, the declining herd immunity to Ortho poxviruses indicates that human monkeypox will probably increase in frequency in the future (World Health Organization, 2022). Based on a study of 338 cases of monkeypox in the Democratic Republic of the Congo in 1980, it was estimated that contact with animals accounted for 72.5% of cases and interaction with other people for 27.5%. However, in the 1990s, the DRC recorded 419 cases, of which 78% were secondary infections and only 22% were original infections, meaning the patient had not reported contact with another monkeypox patient. In 62.3% of instances, transmission was unknown, according to an examination of the Nigerian outbreak data. Of the known instances, 8.2% reported interaction with animals, and 78.3% had an epidemiological connotation with someone who had the same lesions (Bunge et al., 2022).

Since 1984, ecological research has become more focused, but sample collection has mostly been limited to regions of the DRC where human cases are still ongoing. According to these investigations, the virus may spread through animal-human interaction in disturbed "agricultural" areas surrounding communities, which are abundant in terrestrial rodents and fungus (genera Funisciurus and Heliosciurus) (Reynolds et al., 2019).

Pathophysiology

The virus enters the body through the oropharyngeal, nasopharyngeal, or intradermal pathways, multiplies there, and then moves on to the local lymph nodes (Figure 3). Viral dispersion and virus seeding in additional organs follow primary viremia (Zahmatyar et al., 2023).

Signs and Symptoms

Fever, headache, exhaustion, myalgia and lymphadenopathy are the earliest signs of monkeypox, the latter is the primary symptom that sets it apart from smallpox. Mucosal lesions form in the mouth after a day or two, and these are followed by inflammatory skin lesions that extend to the face, including hands and feet. Lesions can range in number from a few to thousands, and the rash may or may not spread to other body parts (McCollum & Damon, 2014).

The lesions are described as hard, deep, and ranging in size from 2 to 10mm. Before crusting, they spend 5-7 days in the pustular phase.

The condition usually goes away 3-4 weeks following the commencement of symptoms, with the crusts forming and sloughing during the next 7-14 days (Weaver & Isaacs, 2008). Within 4 weeks of the commencement of symptoms, the majority of patients fully recover, with the exception of scarring and potential skin discoloration (Sklenovská & Van Ranst, 2018). Patients are no longer regarded as contagious until all the crusts have disappeared (Weaver & Isaacs, 2008). A multinational investigation of 528 monkeypox cases, carried out between April and June 2022, found that the incubation period was 7 days and the most common symptoms were fever, rash, anogenital lesions, and lymphadenopathy (Thornhill et al., 2022).

Planetary Epidemiology of the Disease

In Africa, over 500 definite cases of Mpox were reported between 1970 and 1999. In the DRC, PCR verified 51 Mpox infection cases out of 136 probable cases between 2001 and 2004 (Rimoin et al., 2007). In a reported outbreak of Mpox in the Democratic Republic of the Congo in 2003, all 11 of the confirmed and suspected cases were under the age of 18, and most of them were the inherent of the same facility (Learned et al., 2005). In 2003, the United States had the first MPXV outbreak outside of Africa; no human-to-human transmission was seen, and all cases were patients who were in close proximity to or came into contact with the secretions and excretions of MPXV-infected prairie dogs (Reynolds et al., 2007). In 2005, a few instances were reported in Sudan (Formenty et al., 2010). There was a recorded rise in Mpox in the DRC between 2000 and 2015 (Mandja et al., 2019).

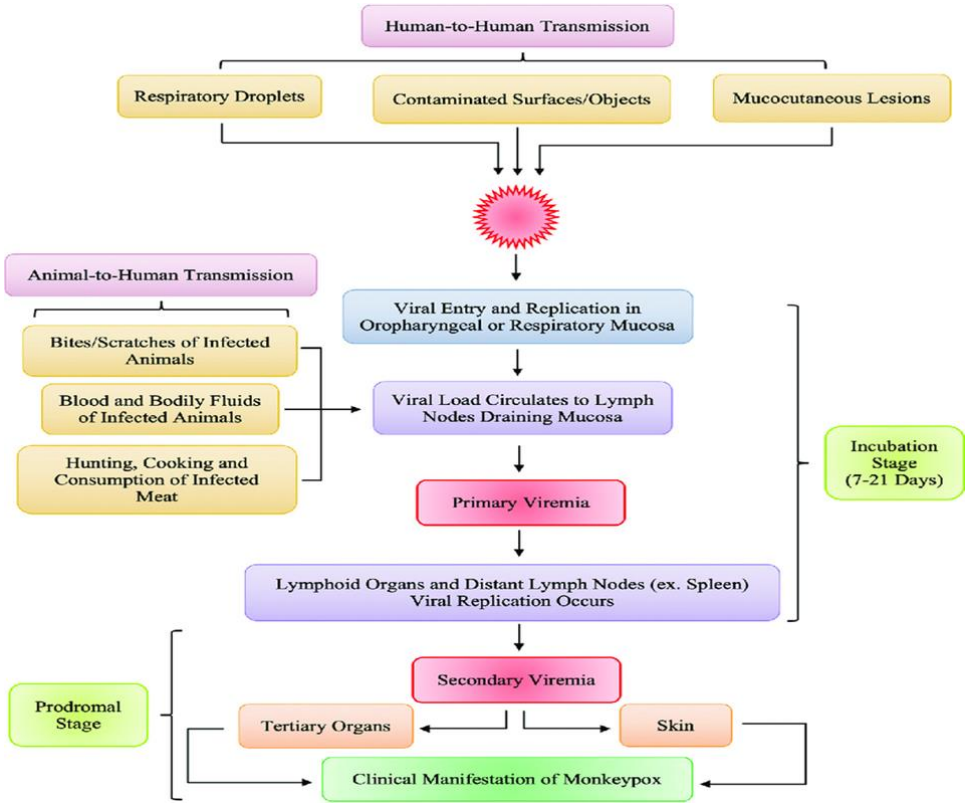

Figure 3: Pathophysiology of Monkey pox

The WHO declared Mpox a Public Health Emergency of International Concern due to the abrupt outbreak in multiple European nations outside of Africa and its following rapid expansion (Khan & Perveen, 2024). Numerous Mpox cases have been detected in non-endemic nations across the globe since May 2022. As of September 30, 2023, 115 countries and territories reported 91123 confirmed MPXV cases and 663 probable cases, including 157 fatalities, to the WHO. People with advanced HIV illness and concomitant varicella-zoster virus infection had a higher incidence of Mpox in Nigeria during the worldwide outbreak in 2022 (Ogoina et al., 2023). The United States of America (n = 30 636), Brazil (n = 10 967), Spain (n = 7611), France (n = 4158), Colombia (n = 4090), Mexico (n = 4062), Peru (n = 3812), the United Kingdom (n = 3805), Germany (n = 3708), and China (n = 1794) join Canada as the top ten reporting nations (Sun et al., 2024). When combined, these nations are responsible for 81.9% of all cases worldwide (Table 1).

Table 1: Prevalence and Mortality of monkeypox disease reported to WHO (2022-23).

Regions	No. of Confirmed Cases	Mortality	References
America	59949	127	(Sun et al., 2024).
African Region	1973	20	(Sun et al., 2024).
European Region	26231	7	(Sun et al., 2024).
Western Pacific Region	2385	0	(Sun et al., 2024).
South–East Asia Region	493	2	(Sun et al., 2024)
Eastern Mediterranean Region	92	1	(Sun et al., 2024).

Diagnosis

Since the clinical characteristics of chickenpox, smallpox, and monkeypox are quite similar, establishing a conclusive diagnosis is crucial to ensuring that the right treatments are put in place to control the illness and stop its spread (Weinstein et al., 2005). Smallpox and cowpox differ significantly from other pox viruses, their histologic characteristics are strikingly similar to those of monkeypox (Alakunle et al., 2020). Monkeypox may be indicated by crop-like, less centrifugally scattered lesions (than smallpox), particularly if there is lymphadenopathy (Pattnaik et al., 2023) since smallpox does not frequently cause lymphadenopath. A crucial diagnostic characteristic that separates monkeypox from smallpox is lymphadenopathy in the submandibular and cervical or inguinal areas (Altindis et al., 2022).

Laboratory Techniques

Lab confirmation is required to provide a conclusive diagnosis, even though clinical features can be useful in distinguishing monkeypox from different infectious roots of vesiculopustular rashes. Monkeypox can be diagnosed using a number of methods, including electron microscopy, serology, and an ELISA technique (Bayer-Garner, 2005).

Skin Biopsy

When skin biopsy specimens from monkeypox patients were examined, they reveal ballooning keratinocyte degeneration, hyperplastic epidermis, and central necrosis. The dermal superficial layers and epidermis both exhibit an inflammatory infiltrate made up of neutrophils, eosinophils, and lymphocytes. The various layers of the epidermis exhibit eosinophilic inclusion bodies and multinucleated giant cells. In the follicular epithelium, follicular involvement and dyskeratotic keratinocytes are also visible. Non-specific histopathologic findings of monkeypox bear striking similarities to those of other contagious viral processes, including cowpox, smallpox, varicella zoster, herpes simplex, and vaccinia (Nakhaie et al., 2023).

Immunochemical Assays

Herpes viruses and poxviruses can be distinguished via immunohistochemical staining. Certain polyclonal antibodies, such as anti-vaccinia murine, are very good in identifying the orthopoxvirus and do not cross-react with the herpes simplex virus. Additionally, there are antibodies against the herpes simplex virus that do not interact with the monkeypox virus (Kulesh et al., 2004). The Orthopox antigen can be found and even identified as the monkeypox virus by monoclonal antibodies that are directed against the virus (Singhal et al., 2022). Five to eight days following a monkeypox infection or vaccinia virus vaccination, orthopoxvirus-specific IgG and IgM can be detected by using ELISA or a lateral flow immunochromatographic assay. Furthermore, IgM is more precise than IgG since residual IgG-memory B cells might persist over time, causing IgG to be positive due to prior exposure or smallpox vaccination (Kulesh et al., 2004).

Molecular Diagnostics

The presence of DNA specific to monkeypox can be found using the PCR approach, which includes real-time PCR examination of a specimen. These techniques are extremely sensitive, and the most effective diagnostic tool for detecting monkeypox at the moment is the real-time PCR approach (Shchelkunov et al., 2011).

Prevention

Since the primary risk factor for the spread of the illness is close contact with an infected individual, using face masks and practicing good hand hygiene can help stop the spread of the illness (Minhaj et al., 2022). In this situation, utilizing a surgical mask is less effective than wearing a N95 mask to avoid transmission (Fleischauer et al., 2005). Because pus and scabs contain high virus titers that enhance the danger of human-to-human transmission, healthcare personnel should wear PPEs to avoid any direct contact with an infected patient (Erez et al., 2019). Furthermore, identifying and isolating those who have gone to regions where monkeypox cases have been reported or who have had sexual contact with infected individuals is crucial (Costello et al., 2022).

Isolating infected individuals until their lesions are completely healed is the most effective method of treating them. Hospitals and local health authorities must make the necessary arrangements for long-term treatment. In many regions of the world, launching educational initiatives to raise public knowledge of illness may also be beneficial (Petersen et al., 2019). Educational initiatives can be crucial in lowering the prevalence of high-risk behaviors, educating the public about disease symptoms, and boosting the prompt hospitalization of patients or their families when signs are noticed (Roess et al., 2011). The ACAM2000 (Post Prophylactic Exposure) and JYNNEOS vaccines are available for those with monkeypox virus exposure or those who are at the high risk of occupational exposure (Afshar et al., 2022). Public health officials in the U.S, U.K, and Singapore have safely employed these vaccines (Erez et al., 2019). Reducing worldwide zoonotic diseases, population-level surveillance, breaking down transmission chains, and developing and disseminating effective vaccines and antivirals should all be part of the collective strategy to stop future monkeypox outbreaks (Chavda et al., 2022).

Treatment

At present, there is no specific treatment for the disease's fundamental cause. The suggested approaches include symptomatic therapy and superadded infection prevention (Chavda et al., 2022). Monkeypox-specific antivirals are not available yet but brincidofovir and tecovirimat are the treatment options of monkeypox and the duration of treatment is14 days (Zovi et al., 2022).

Conclusion

During the monkey pox outbreak in 2022, Health care systems were disrupted severely due to COVID-19 pandemic. Now it’s not an uncommon viral sickness which is only found in the forested areas of Central and Western Africa, as evidenced by the expansion of the disease

exterior of Africa. In order to prevent the emergence of a new, highly contagious disease, the outbreak has once again focused on the importance of early diagnosis and preventive measures. Establishing the disease's clinical features, choosing appropriate diagnostic techniques, and developing strategies for its effective treatment and prevention across Central and Western Africa's forested areas are therefore crucial.

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