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A Comprehensive Review on Rising Concern of Transmission Potential of Monkeypox Virus on Healthcare System

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ABSTRACT: Over the past few years, the countries of the world have been afflicted with numerous infectious ailments. As the terror of the COVID-19 disease widespread decreases, nations throughout the world are facing the terror of the epidemic surrounding the pervasiveness of the geographical spread of human monkeypox cases worldwide. Thus, several approaches to decimate the rising spread of the monkeypox virus (MPXV) are warranted. MPXV cases received global attention during the 1970s, emanating from Africa has fully-fledged to be a universal concern with MPXV cases reported in Israel, Singapore, the United Kingdom, and the United States. Monkeypox appears as a zoonotic viral disease that is instigated via the monkeypox virus recognized as the most critical orthopoxviral infection in humans. Transmission of the monkeypox virus to human beings is alleged to occur via direct exposure to infected animals or it can probably be transmitted via consuming infected meat, or blood. The transmission from human to human takes place through the respiratory route (droplets), virus-contaminated material, and direct contact (skin-to-skin or sexual). This disease may be caused several difficulties including, headache, fever, malaise, back pain, rash, and lymphadenopathies. Presently, there is no proven therapy for its treatment, thus monkeypox virus is considered a major threat to global health security. In this review, we discussed the transmission potential of the monkeypox virus on the healthcare system, its epidemiology, mode of transmission, and different diagnostic, preventive, and treatment approaches.

INTRODUCTION

Viruses endure being responsible for a huge numeral of medically significant emerging and re-emerging diseases, as well as several human beings and animal infectious illnesses. They cause lethal and most frightening human illnesses, and their capability to spread quickly makes them significant benefaction to comprehensive infectious disease mortality and morbidity [1].

Monkeypox virus (MPXV) is an extremely pathogenic orthopoxvirus that occurs in humans and causes clinical symptoms similar to smallpox. Prodromic symptoms last for 2 to 4 days and cause headache, fever, back pain, fatigue, and lymphadenopathy. Fever subsides three days following the inception of a smallpox-like rash that starts on the face and rapidly feasts over the whole body centrifugally, including the oral mucosa, palms, soles, and genitalia. The rashes last for 2-4 weeks, beginning with macules and progressing to papules, vesicles, pustules, and crusts finally [2-4], as described in **Fig. 1**.

Various complications of the monkeypox virus include tonsillitis, encephalitis, pharyngitis, sight-threatening keratitis, conjunctivitis, and severe dehydration caused by vomiting and diarrhoea [2]. Monkeypox and smallpox are closely related

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viruses. From research investigations, it is predicted that infections caused by the monkeypox virus would also be treated by the smallpox vaccination. It has been found that the probability of the monkeypox virus in previously immunized people can be reduced by smallpox vaccination [5, 6]. The key differences between monkeypox, smallpox and chickenpox [7-9] are shown in **Table 1**.

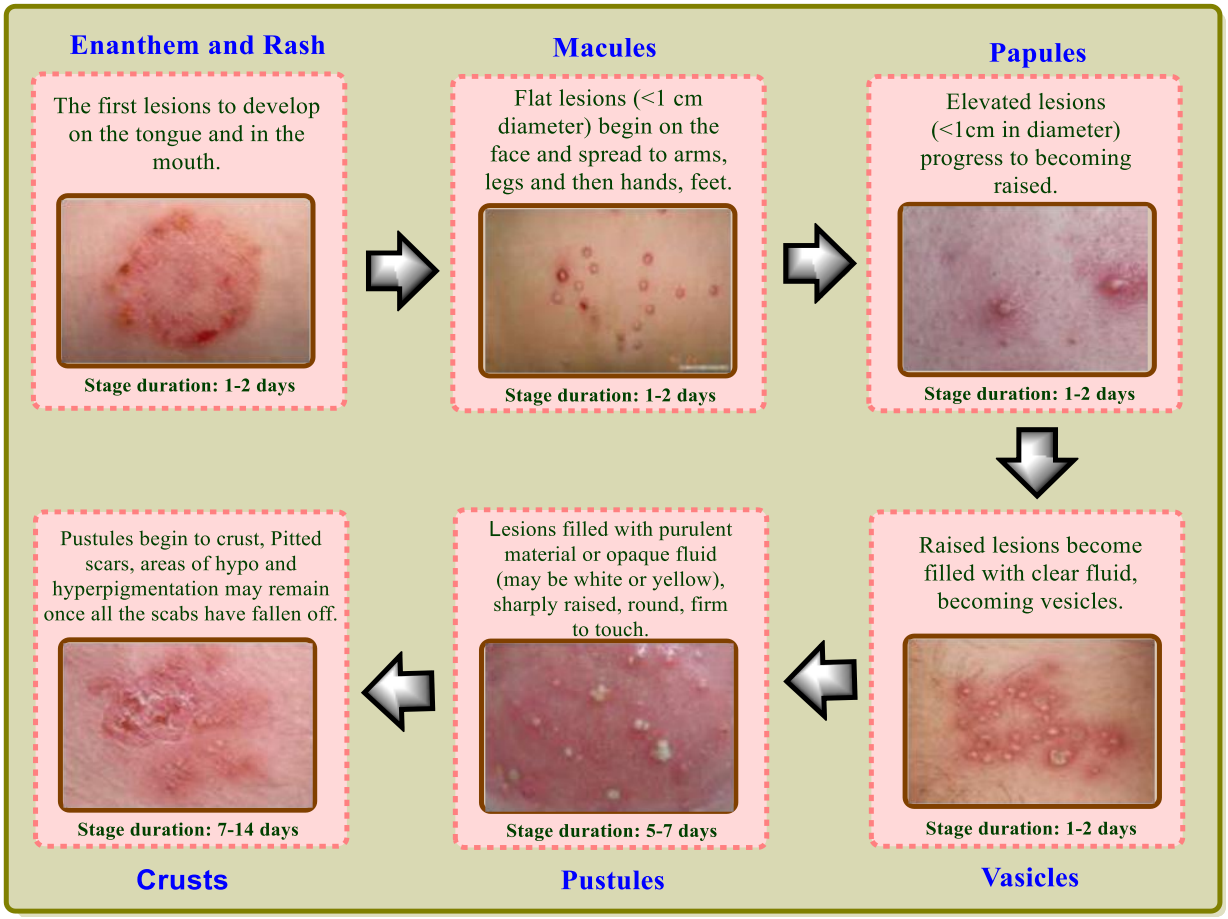

Fig. 1. The stages of vesicular pustular rash in monkeypox patients.

Table 1. The characteristic features of monkeypox, smallpox and chickenpox viruses.

Illness	Monkeypox	Smallpox	Chickenpox
Pathogeny	Monkeypox virus	Smallpox virus/variola virus	Varicella-zoster virus
Spread through contact with exotic animal	Yes	No	No
Incubation Period	5 to 21 days	7 to 17 days	10 to 21 days
Clinical Manifestations	Fever (>38.5°C); 1 to 5 days before the rash, intense headache, exhaustion, asthenia, chills, myalgia, lesions, back pain, and lymphadenopathy.	Fever (>40°C), vomiting, chills, back pain, headache, and abdominal pain.	Fever (up to 38.8°C); 1-2 days before the rash, sore throat, chills, vomiting, and exhaustion.
	Type of centrifugal: macules-papule-vesicles, and progression	Type of centrifugal: maculopapular (face and neck),	Type of centripetal: round edgy blister, rash, mounds, spots,

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Rash	starts from the face and extremities, and spread all over the body; The lesions are habitually in one stage (each stage shows slow progression).	vesicular and pustular, and progression originates from the face, forearms, and oral mucosa. The lesions are developed in the same stage (each stage show slow progression).	scabs, and blisters appear simultaneously, and progression originates from the face and trunk extremities. The lesions are developed at several stages of the human body (i.e., fastest progression).
Susceptible Population	Unvaccinated smallpox vaccine	General	6 to 9 years of age.
Course of Diseases	2 to 4 weeks	12 to 20 days	5 to 7 days
Laboratory diagnosis:			
DNA detection (e.g., PCR)	Monkeypox virus	Variola virus	Varicella zoster virus (VZV)
Electron microscopy	Poxvirus particle	Poxvirus particle	Herpes virus
Serology	Orthopoxvirus and monkeypox virus antibodies	Antibodies of orthopoxvirus and variola virus.	Varicella

OUTBREAKS/EPIDEMIOLOGY OF MONKEYPOX VIRUS

This zoonotic virus was discovered in 1958 in the colonies of monkeys, preserved in a Danish research laboratory, which causes pox-like disease. As a result, the illness is termed as 'Monkeypox', but it is alleged to be spread to human beings via wild animals such as rodents or infected people [10, 11]. The first confirmed human case, however, occurred in 1970, when the virus was isolated from a 9-month-old child in Zaire, now known as the Democratic Republic of Congo (DRC), who was suspected of having smallpox disease [12]. Monkeypox has since become pervasive in the DRC and has spread to several other African countries, primarily in West and Central Africa. A total of 10 cases of MPXV were reported between 1970 and 1986, from Western African countries, including Nigeria, Sierra Leone, Liberia, and Côte d'Ivoire, and a total of 394 cases of MPXV were reported from the Congo Basin countries of Cameroon, Central African Republic and Zaire (DRC) [13].

Monkeypox was previously restricted to the rainforests of Western and Central Africa. However, in 2003, the first case of monkeypox in the Western Hemisphere was reported outside of Africa, where 11 people from the United States were in close contact with infected prairie dogs [14]. This may be allied to the increased interface between human beings and monkeypox virus carriers. Nigeria Centre for Disease Control reported that a suspected case of MPXV in an 11-year-old child was found in 2017, having an 11-day history of fever, malaise, and the liberal advent of a vesiculopustular rash on his skin, oral and nasal mucosa, and generalized lymphadenopathy [15].

A total of 4 people in the UK were diagnosed with travel-associated MPXV in 2018, with onward transmission to 3 more people [16]. In 2019, the prevalence of MPXV in 38-year-old people has been found in Nigeria who had travelled to Singapore [17]. The cases of MPXV have been continuously expanding over the following decade. There was a total of 19,065 MPXV cases from 2010 to 2019 in Africa, and 6 cases of MPXV were found, where MPXV has not been widely spreading [18]. However, global attention has been recently focused on the monkeypox virus after the confirmed case of MPXV in the West African clade reported in the UK in May 2022 and thereafter in multiple countries [19].

The outbreak of monkeypox spreads across many countries since the early month of May 2022. A total of 9 MPXV cases were first reported in the UK on May 7, 2022. The United Kingdom Health Security Agency (UKHSA) testified to an ancestral gathering of 02 MPXV cases on May 14, 2022, in the UK. About 3413 cases of MPXV and 1 death were testified from January 1, 2022, to June 22, 2022; recognized by WHO (World Health Organization) from around fifty countries in 05 regions of WHO, with the European region accounting for 86% (2933/3413) of MPXV cases. There were 3340 confirmed MPXV cases from May 3, 2022, to June 22, 2022, from the 04 WHO regions and 42 member states, that were not endemic to MPXV [7, 20].

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WHO reported a total of 15,734 cases of MPXV in 75 countries across five continents, including children on July 21, 2022. These cases are almost double the cases reported in the earlier reports, which were published about two weeks prior on 9th July 2022, which emphasize the continual spread of MPXV. Epidemiological findings from previous outbreaks of MPXV showed that the rate of secondary attack would be higher than 12.3% among the smallpox-unvaccinated people with symptoms of monkeypox. This rapid terrestrial spread of MPXV indicates the possibility of a public well-being emergency of global apprehension [21].

MONKEYPOX VIRUS STRUCTURE/ETIOLOGY

The morphology, size, and genomes of the monkeypox virus (MPXV) are found to be similar to the Variola virus (VARV); however, it has a more extensive host range, allowing it to infect a variety of species including, monkeys, rodents and human beings. The people infected with MPXV exhibit similar clinical manifestations as that of VARV infection [22]. Despite being a DNA virus, the entire life cycle of MPXV spends in the infected cell's cytoplasm. The monkeypox virus is classified into two genetic clades as Western African and Congo Basin clade (Central African). The Congo Basin clade has been thought to be extremely infectious and to have previously caused severe illness.

MPXV is one of the most complex and largest animal viruses, with an electron microscopy length of 200 to 250 nm. The virus is made up of four major constituents including, the outer lipoprotein envelope, outer membrane, lateral bodies, and the core. The outer lipoprotein membrane of virions is geometrically corrugated, and the core is hollowed and comprises a large double-stranded DNA genome with lateral bodies on both sides. The size of its genome is about 197 kb and encodes around 200 proteins. An inverted terminal repeat is an oppositely oriented sequence but identical found at the terminal of the genome. The genome is made up of 190 nonoverlapping open reading frames and has closed hairpins on its ends [7, 23]. The structure of the monkeypox virus [24] is illustrated in **Fig. 2**.

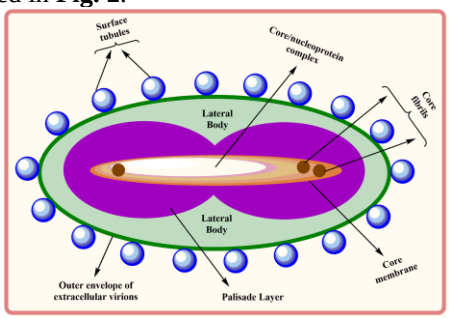

Fig. 2. Structure of monkeypox virus.

PATHOPHYSIOLOGY/VIROLOGY OF MONKEYPOX VIRUS

Monkeypox virus is a kind of double-helix DNA virus with a lipoprotein membrane, belonging to the family of Poxviridae, subfamily name-chordopoxvirinae, and genus name-orthopoxvirus [20]. An antique virus family, Poxviridae found in various species including, mammals, birds, insects, and reptiles, and is alleged to cause visible "pox" preceding vertebrate-invertebrate discrepancy [25].

The genome of MPXV encodes all proteins which are essential for the replication of viral DNA, their transcription, egress, and virion assembly. The housekeeping function genes are extremely preserved among orthopox viruses and are found in the middle area of the genome, whereas virus-host interaction genes are less preserved and found in the termini region [26]. Even though, MPXV has a lower rate of mutation; the adaptive mutations of the virus may ensue under certain selective pressure, which may have increased its transmission potential [9].

MODE OF TRANSMISSION

The precise method of transmission of MPXV to human beings is unknown. The transmission from animal-to-human beings primarily occurs while handling MPXV-infected animals, either directly (i.e., by bite, touch, or scratch), or indirectly. It is assumed that the virus enters the human body via the respiratory tract, broken skin, and mucous membranes of the eyes, nose, or mouth. Secondary, transmission from human-to-human beings is most common, most likely via body fluid, direct/indirect contact with lesion material or respiratory droplets, and infected surfaces such as linens or clothes. Long-term contact with patients puts the staff of hospitals and their families at higher risk of infection [12].

The immune-histochemical assays for orthopox viruses in prairie dogs revealed that viral antigens are plentiful in the lesion's epithelial cells in the tongue and conjunctiva, but few in amounts in the connective tissues, fibroblasts, and adjacent macrophages. The electron microscopy showed the viral replication in the tongue and lungs, which implies that mucocutaneous exposures and the respiratory tract both may be imperative routes of MPXV transmission among human beings and rodents [27]. The routes of transmission associated with the MPXV [3, 28] are described in **Fig. 3.**

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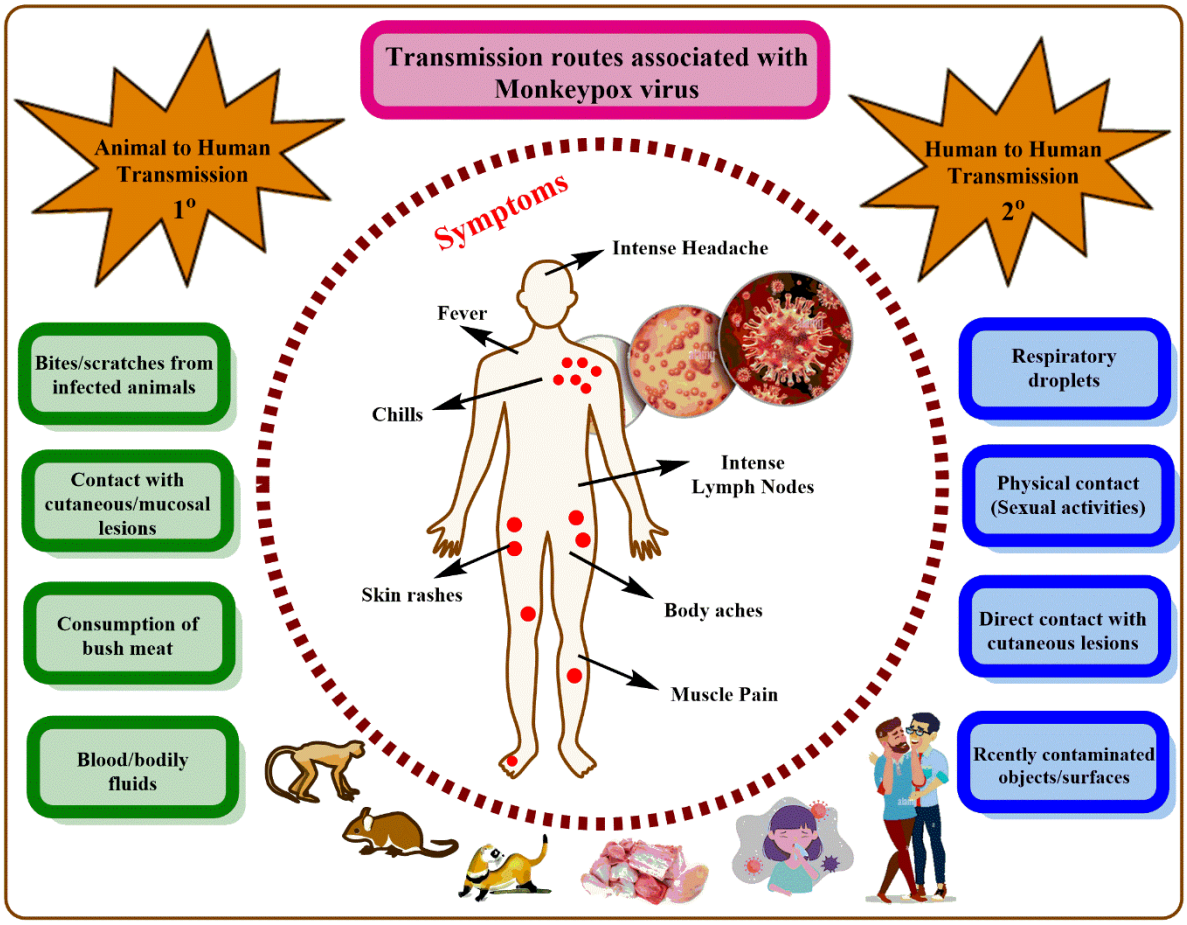

Fig. 3. Transmission routes associated with the monkeypox virus.

DIAGNOSTIC, PREVENTIVE AND TREATMENT APPROACHES

The diagnosis, clinical recognition, and prevention continue to be difficult in resource-limited endemic regions where cases of MPXV are found. Diagnostic assays are critical components in determining an orthopoxvirus infection. Traditional approaches like viral isolation from clinical specimens, electron microscopy, and immunohistochemistry are reasonable methods, but they necessitate innovative technical expertise and sophisticated laboratory requirements. The specimens can be tested for the existence of orthopoxvirus or MPXV in a lesion with the help of real-time PCR (Polymerase chain reaction). These methods are extremely sensitive and capable of detecting viral DNA [29]. On the other hand, serological methods that evaluate anti-orthopox virus, immunoglobulin M (IgM), are widely useful for diagnosing recent retrospective infections in people, who have previously been vaccinated [30].

MPXV has no well-defined drug or vaccine; it is treated as a severe syndrome by management and precautions of their symptoms and complications. However, in some countries like the US, JYNNEOS®, a licensed vaccine (monkeypox vaccine and Smallpox, live and non-replicating), has been advised for pre-exposure vaccination of people at risk of occupational acquaintance to orthopox viruses. The other vaccine, ACAM2000 (consisting of live Vaccinia virus) is also permitted for those above the age of 18 years usage in adults, who are at excessive risk of having smallpox. From research findings, it has been revealed that the smallpox vaccines are 85% protective against MPXV [20, 28]. The general strategies used for the eradication and treatment of the monkeypox virus [6], are described in Fig. 4.

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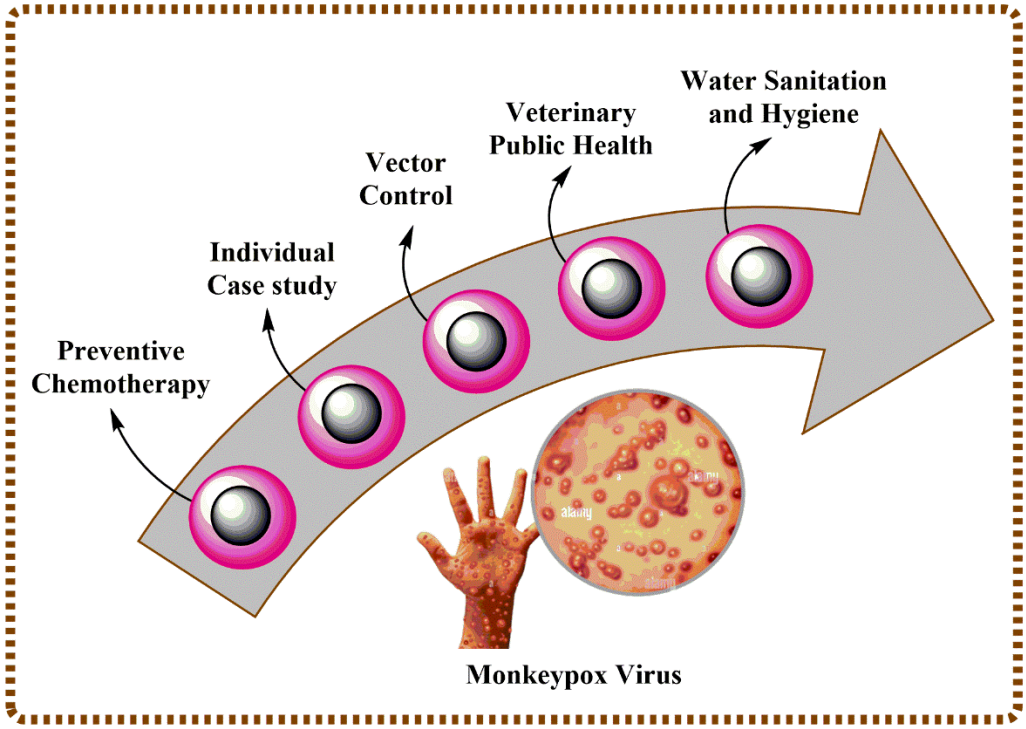

Fig. 4. General strategies used for eradication and treatment of monkeypox virus.

Furthermore, in 2022, the European Medical Association (EMA) approved an antiviral drug tecovirimat used in smallpox, for the treatment of MPXV [20]. The US Centers for Disease Control and Prevention Center of US allows compassionate usage of kept tecorvir in the treatment of MPXV during its outbreaks. Another antiviral drug, Brincidofivir (tembexa), is permitted by the USFDA (US Food and Drug Administration) to cure smallpox in children and adults, including infants. The US CDC has also approved the use of cidofovir (vistide) to treat orthopox viruses including monkeypox during outbreaks [7].

CONCLUSION

The re-emergent and rising monkeypox cases have added to the strain on healthcare systems. Monkeypox is a zoonotic disease instigated via the monkeypox virus (MPXV), an orthopoxvirus that is related to the variola virus. Transmission of the monkeypox virus from human-to-human is well documented, which includes household and nosocomial spread. Despite the availability of vaccines, studies have shown that smallpox vaccination is almost 85 % productive in the prevention of MPXV. Global challenges include a deficiency of well-operative surveillance tactics for early findings; a general deficiency of knowledge and awareness of the monkeypox disease; and a lack of medical facilities that are previously overburdened by coronavirus cases. As a result, the role of WHO (World Health Organization) in preventing the spread of MPXV is very critical. Upcoming research investigations should be focused on integrative technologies that merge human beings, animals and ecological efforts to learn the different mechanisms of MPXV and offer appropriate solutions to safeguard healthcare system.

AUTHOR CONTRIBUTIONS

RG and MD: Wrote the manuscript; SG: Data collection; RKG: Read and evaluate the different version of the draft till finalization. All authors analyse the whole manuscript and give consent for publication.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. Journal and Publisher will not be responsible for any copyright infringement and plagiarism issue.

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AVAILABILITY OF DATA AND MATERIALS

All the key information is already available in the manuscript, still, authors are ready to share the raw data, if the proper channel for the inquiry will be followed which will be routed through journal and affiliation authorities.

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