

# A Systematic Review on Human Monkeypox Virus Disease and Infection in Pregnancy

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## Abstract

The monkeypox virus (MPXV) has become a dangerous zoonosis. The fast spread of MPXV occurred in the last two years. The number of cases remarkably increased in 2022. The reasons behind the sudden increase in MPXV cases are multifactorial. Monkeypox (MPOX) a viral zoonotic illness, is caused by MPXV. It is an enveloped, linear, double-stranded DNA virus. MPXV transmission may take place by direct contact with humans or animals. This article summarizes a better understanding of the spread of MPXV infections. Pregnant and breastfeeding mothers require a high level of care and precaution against this virus as the infection may transmit during pregnancy from mother to fetus and during breastfeeding to the infant. Clinical management of monkeypox in pregnancy is also reviewed in this article.

**Keywords:** Monkeypox Virus, Orthopoxvirus, Treatment, Pregnancy

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## INTRODUCTION

Over the past ten years, cases of new deadly viral diseases have been ongoing.<sup>1</sup> The monkeypox outbreak in 2022 affected various countries in both endemic and non-endemic regions.<sup>2,3</sup>

Monkeypox (MPOX), a rare zoonotic viral illness, is caused by the monkeypox virus (MPXV). MPOX virus belongs to the family Poxviridae, the Orthopoxvirus genus, and the subfamily Chordopoxvirinae. Before the year 2022, MPOX human cases were especially prevalent in Central and West Africa.<sup>4,5</sup> The primary MPOXV outbreaks were reported in 1970, 1996–1997, 2003, and 2018. The MPOX disease is milder, with symptoms like those of smallpox, including swollen lymph nodes, high fever, headache, and skin rashes. The skin rashes developed into pus-filled blisters that quickly spread across the entire body, including the face, before they ruptured and crusted after a few days. MPOX is a self-limiting condition that has a 2 to 4-week symptom duration. The mortality rates of MPOX cases range from 1 to 10%.<sup>6,7</sup> MPOX cases are reported in both Europe and North America. Since the first case was officially reported in Europe in early 2022, more than 800 suspected or confirmed MPOXV cases are reported in 20 non-African nations.<sup>8</sup> The first MPOXV patient was diagnosed in 2022 in the United Kingdom (UK) after travelling from Nigeria; however, some of the recent confirmed cases had no travel history to either Africa or Nigeria, indicating that the Monkeypox virus had started spreading within the community.<sup>9</sup> Most cases documented in non-endemic nations are from bisexual, gay, and other males who were involved in sex with males. The MPOX outbreak has afflicted human settlements with no travel connections to an endemic African location, in contrast to the earlier isolated cases.<sup>10</sup> Instead of persistent human-to-human transmission, MPOXV penetrates communities in endemic contexts by zoonotic transmission.<sup>11,12</sup> There is no confirmation about the reservoir host. Tiny mammals like elephant shrews and rodents may contribute to the natural history of the virus.<sup>13</sup> Even though the vaccine used for smallpox shows 85% protection against MPOXV,<sup>14</sup> inoculation against the smallpox virus was not offered since 1980,<sup>15</sup> when the WHO

declared the smallpox virus to be extinct. MPOXV-specific therapeutic agents and immunization are also lacking. A thorough study of the biological traits and pathogenicity of MPOXV is required to stop the spread of MPOX outbreaks. Here, we highlighted the origin, biological characteristics, epidemiology, pathogenicity, signs and symptoms, laboratory diagnosis, prevention, and treatment of MPOX in humans and pregnant women.

### History of Monkeypox

Monkeypox is a formerly neglected zoonotic disease indigenous in Central and West Africa. MPOXV was discovered for the first time in 1958 in some captive areas of cynomolgus monkeys. The monkeys were brought from Africa and housed in Copenhagen, Denmark. The virus was like smallpox.<sup>16</sup> The first human case of MPOX was reported in the Democratic Republic of the Congo (DRC) in 1970. Tiny forest mammals were found to be the primary carrier of virus transmission and it was later found in different species, like squirrels, rats, prairie dogs, and mice.<sup>17,18</sup> In 2003, 47 cases of MPOX outbreak outside Africa were recorded in the six states of the USA.<sup>19,20</sup> Some other cases reported outside of Africa were from Israel, Singapore, and the UK. The West African clade and the Central African clade are the two subvariants of the monkeypox virus. The Central African Clade is less aggressive than the West African Clade. The Western African Clade, have an estimated death rate of 1 to 3%, and the Central African Clade has a mortality rate in the range of 10%.<sup>18</sup> Although the method of zoonotic transmission of monkeypox to humans is still unknown, the majority of monkeypox infections in humans were spread by contact with small forest animals.<sup>16</sup> Following the 2003 US outbreak, a study found that the leading causes of 47 human MPOX cases were brought on by contact with sick animals, bites, scratches, cleaning animal cages, or contact with sick animals' bedding.<sup>19-21</sup> However, some infected people claimed that the presence of infected animals in the same room may cause disease. Similar to the closely related smallpox virus, it is believed that contact with large respiratory droplets and contaminated bodily fluids causes most of the human-to-human transmission.<sup>22</sup> The monkeypox virus may also be present in semen and other bodily fluids,

according to recent findings.<sup>23</sup> However, more research is needed to determine how seminal fluid affects the spread of the monkeypox virus. It is unknown whether pre-symptomatic and asymptomatic carriers exhibit Contagiosity.<sup>19</sup> Anecdotal comments from frontline healthcare professionals posted on social media also imply that an infected person may have few or no previous symptoms, which may transmit the virus to another person.<sup>24</sup>

### **Biological Characteristics of MPOXV**

The MPOX virus particles are 200–250 nm in size and oval or brick-shaped.<sup>25</sup> External enveloped virus (EVV) and intracellular mature virus (MV) are the two infectious viral particles produced due to poxvirus replication. The envelope is made up of lipoprotein that surrounds the core of the virus and the lateral body. It contains specific proteins and is present on the surface of the MV. When a cell is ruptured, MV is released which is generally stable in the outer environment. It is mainly spread from the animal-to-animal transmission. A lipid membrane is covered around MVs to create EV, which is released through exocytosis. It comes from endosomes or the transport Golgi apparatus.<sup>26</sup> The genome of MPOXV is double-stranded, linear, and around 197 kb in size.<sup>27</sup> MPOXV strains encode more than 190 open reading frames (ORFs). The virus's non-conserved genes are typically found in ITRs at both ends, which are host-and poxvirus-specific. However, four viral proteins (D8, A27, A26, and H3) promote MV adsorption on the surface of cells for the vaccinia virus (VACV), which is most likely MPOXV. MPOXV can last a prolonged period at 4°C and is resistant to drying and cold temperatures.<sup>25</sup>

### **Distribution of MPOX**

WHO recorded 16,016 cases of monkeypox from 1 January 2022 to 22 July 2022, with laboratory confirmation and five fatalities from 75 countries. DRC provides the number of suspected cases reported starting in 2022 in (Table 1 and Table 2) highest number of monkeypox cases is given.<sup>26-28</sup>

### **Sources of infection**

Monkeypox is a zoonotic infectious illness that typically manifests intermittently in tropical

forests in Central and West Africa.<sup>29</sup> MPOXV transmits by both direct touch and vast droplets of inhaled fluid. The vaginal, anal, or oral sex with an MPOX-infected person may spread this virus.<sup>30</sup> The Vervet monkeys from Kenya, Chimpanzees, African elephants, wild bears, antelope, Gambian-poached rats, pet prairie dogs, West African squirrels, and anteaters are just a few examples of specific animal reservoirs.<sup>31,32</sup>

### **The mode of transmission**

The MPOX virus can spread when an individual meets an infected animal, infected human being, or virus-contaminated items. The transmission of MPOXV is possible from both animal-to-human and human-to-human contact, as shown in Figures 1 and 2, respectively.<sup>18</sup> The placenta of a mother can also transmit the virus to the fetus. MPOXV transmission also occurs through direct contact with the blood, other body fluids, or cutaneous or mucosal lesions from bites or scratches of infected animals, treating wild animals, or using items derived from infected animals.<sup>33,34</sup> Direct contact with infectious ulcers, scabs, human fluids, or objects such as clothing or linen is the primary method of transmission for monkeypox. Respiratory secretions can also spread during prolonged contact with the face. Additionally, MPOXV can transmit through close physical contact, such as kissing, embracing, or touching monkeypox-infected body parts.

According to one study, secondary transmission caused up to 28% of cases in the DRC.<sup>36</sup> Although the illness is not typically thought of as sexually transmitted, intimate contact has been shown to cause inter-human transmission.<sup>37</sup> As a result, the possibility of communal transmission exists. The mode of transmission of MPOXV is shown in Table 3.<sup>38</sup>

### **Monkeypox in pregnancy**

The MPOXV can be passed from mother to fetus during pregnancy or from mother to infant during and after birth through intimate contact. MPOX infection during pregnancy can cause unfavourable pregnancy outcomes, such as spontaneous pregnancy loss and stillbirth. Additionally, recorded cases include preterm birth and MPOX infection in newborns. Human monkeypox virus can cause a severe congenital

infection and pregnancy loss.<sup>39</sup> Table 4 summarised some data on four pregnant women from DRC who got infected with MPOXV during pregnancy.

### Guidelines and Treatment of Monkeypox in Pregnancy

There are no formal guidelines for pregnant women exposed to MPOXV. Pregnant women's immune systems change during pregnancy therefore, they are more susceptible to exposure to monkeypox virus. Pregnant, recently pregnant, or nursing women should be

offered therapy for MPOX. However, considering the lack of data on treatment effectiveness, the treatment choice will depend on the disease's stage and severity. The choice of whether to treat and monitor a pregnant person as an outpatient or an inpatient should be made individually after the risks and benefits of the treatment have been reviewed with the patient through shared decision-making. WHO has given clinical consideration for monkeypox in pregnant and breastfeeding women. The data regarding the effect of MPOX in pregnant and breastfeeding

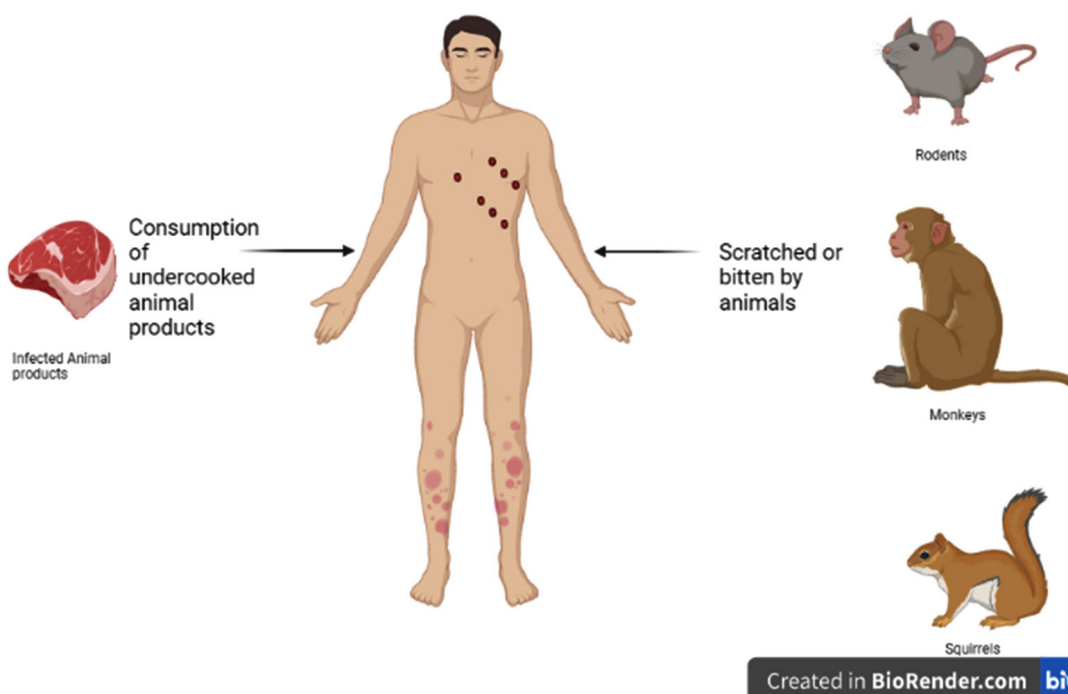
**Table 1.** Human monkeypox cases in the Democratic Republic of the Congo (DRC)

Previous data of 10 Years	Suspected	Confirmed	Death
1970 to 1979	nil	48	8
1980 to 1989	nil	357	36
1990 to 1999	nil	520	3
2000 to 2009	10027	139	1
2010 to 2019	18788	283	30

**Table 2.** Highest number of Monkeypox cases in 2022 in five countries

Country Name	No. of cases
Spain	3125
United States of America (USA)	2316
Germany	2268
The United Kingdom (UK) and Northern Ireland	2137
India	04

### TRANSMISSION OF MONKEY POX VIRUS BY ANIMAL TO HUMAN BEINGS

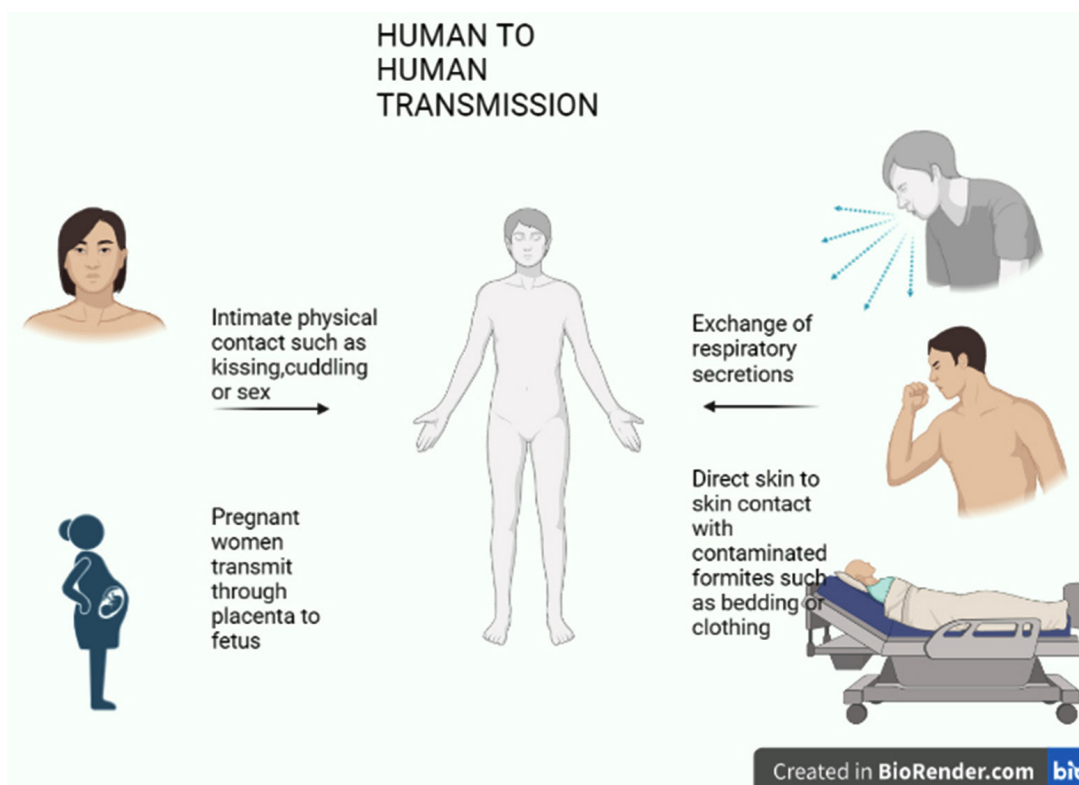


**Figure 1.** Represents the transmission of the monkeypox virus by animals to human beings.<sup>33,34</sup>

women are lacking. Pregnant women with MPOX virus infection exhibit similar early signs of fever, headache, lymphadenopathy, malaise, sore throat, cough, and rash, to the non-pregnant women with MPOX virus infection. The MPOX-infected pregnant women should be isolated for 21 days. The women should be monitored for body temperature, blood pressure, and rashes. Ultrasound fetal surveillance should be conducted to check the growth of the fetus. Some outcomes resulting from the review of these pregnant women infected by the monkeypox virus include vertical transmission, maternal morbidity, miscarriage, severe congenital disorder, and no maternal death. Tecovirimat (antiviral drug) and vaccinia immune globulin intravenous (VIGIV) is safe for treating Human Monkeypox infected pregnant women in severe conditions.

Tecovirimat drug is approved by USFDA for pregnant women. Tecovirimat has no embryotoxic or teratogenic effect in animals. It is unknown whether tecovirimat use during pregnancy helps to prevent congenital MPOX.

Even though the drug was present in breast milk in animal trials, it is uncertain whether the levels of tecovirimat released into breast milk are enough for treating a breastfeeding child with MPOX. Therefore, breastfeeding children with MPOX should get independent treatment as required. Cidofovir and brincidofovir are potential alternative antiviral medicines for treating MPOX in the general population. However, research on animal reproduction found evidence that they were teratogenic. As a result, women who are in the first trimester of pregnancy should not take these drugs to treat MPOX. It is unknown whether cidofovir and brincidofovir are found in breast milk; therefore, they should not be used by nursing mothers due to the possibility of significant adverse effects on the infant. The first line of treatment in pregnancy should be tecovirimat. In the second or third trimester, cidofovir may be in special cases. However, nephrotoxicity is a significant side effect of cidofovir.



**Figure 2.** Represents the transmission of the monkeypox virus by infected humans to normal human being.<sup>33-35</sup>

It is unknown whether vaccine immune globulin intravenous (VIGIV) can harm a fetus during pregnancy or impact future fertility because no animal reproduction research is conducted on it. Immunoglobulins, however, are frequently used during pregnancy for a long time without appearing to have any unfavourable consequences on the developing fetus. Therefore, each patient should be examined for the risks and benefits of receiving VIGIV. The excretion of VIGIV in human milk is unknown. Attention should be taken when giving VIGIV to breastfeeding people because many medications secrete in human milk.

Vaccination with ACAM2000 is contraindicated in pregnant or nursing women due to the danger of miscarriage, congenital abnormalities, and vaccinia virus infection in fetuses and new-borns, as well as the availability of a non-replicating viral vaccine. MVA-BN is a third-generation smallpox vaccine that has been approved in the USA (JYNNEOS), Canada (IMVAMUNE®), and Europe (IVANEX®) and is safer as compared to other antivirals because it contains non-replicating viruses and comparatively fewer adverse effects in pregnancy and breastfeeding.<sup>39</sup>

**Diagnosis of monkeypox**

A feverish prodrome, the onset of lymphadenopathy, a generalized rash with

well-circumscribed lesions at the same stage of development, and a pattern of centrifugal dispersion are all characteristics of typical MPOX (as shown in Table 5). The recommended diagnostic samples are collected by vigorously swabbing skin, fluid, or crusts directly from the rash. Testing can be done on oropharyngeal, anal, or rectal swabs in the absence of cutaneous lesions. Blood testing is not advised. The time of incubation for MPOX is 3–17 days. A person may feel fine and not have any symptoms during this time. Usually, the disease lasts two to four weeks.<sup>40-41</sup>

**Prevention and Treatment of Monkeypox**

MPOXV spread can be prevented by adopting infection prevention and control approaches. Immunization is one such approach. Persons involved in sex with multiple partners or queer sex are prone to get infected. A person infected with MPOXV should be isolated to prevent the spread of the virus to healthy persons. The MPOXV has been found in semen however, the spread of MPOXV through sex is not confirmed. However, direct contact like touching, kissing, or sexual intercourse should be avoided with infected persons.<sup>42</sup> The treatment of MPOX includes vaccines and antivirals, as shown in Table 6.

**Table 3.** Mode of Transmission of monkeypox virus in recent years

Year	Central countries	Western countries	Other countries
1970 – 1979	Cameroon: not known DRC: Both	Liberia: not known Nigeria: not known Nigeria: human-to-human Sierra Leone: Not known	Nil
1980 – 1989	CAR: Animal to human DRC: Both Gabon: unknown	Ivory Coast: Not known	Nil
1990 – 1999	DRC: Both Gabon: not known	Nil	Nil
2000- 2009	DRC: Animal to human RC: Animal to human	Nil	Nil
2010–2019	CAR: Both DRC: Animal to human RC: not known	Nigeria: Both Sierra Leone: not known Sierra Leone: Animal to animal	Israel: Animal to human Singapore: Animal to human South Sudan: Human-to-Human UK: Human to human US: Animal to human

Abbreviation: CAR: Central African Republic; RC: Republic of Congo



**Table 4.** Observations of conditions of some pregnant women infected with the Human monkeypox virus from DRC in 2007 to 2011

Pregnant women	Condition after infection with monkeypox virus
1 <sup>st</sup> woman	Spontaneous early miscarriage
2 <sup>nd</sup> woman	Spontaneous early miscarriage
3 <sup>rd</sup> woman	Second-trimester loss (18 weeks gestation)
4 <sup>th</sup> woman	The fetus had generalized skin rashes and monkeypox DNA present in fetal tissue, umbilical cord, and placenta

**Vaccination**

There is not yet a specific vaccine available to prevent MPOXV infection. According to certain reports, vaccinating against smallpox offers 85% protection from MPOXV.<sup>42,43</sup> IMVAMUNE® (Canada), IVANEX® (Europe) or JYNNEOS (USA) is a replication-deficient, attenuated, third-generation modified vaccinia Ankara Bavarian Nordic (MVA-BN) vaccine that has also received approval from the European Medicine Agency (EMA) and the Food and Drug Administration (FDA) for the prevention of MPOXV and smallpox virus in adults

**Table 5.** Diagnosis of MPOXV.<sup>40,41</sup>

Diagnosis tests	Description
1)Genetic methods (RT-PCR)	Detects the presence of MPOXV and its specific DNA signatures
2)Phenotypic Methods (By clinical diagnosis)	Live virus is taken from the specimen of the patient and grown and characterized
3)Electron Microscopy	A brick-shaped particle confirms the presence of pox virus
4)Immunological methods (ELISA)	Serological detection of MPOXV through peptide-based ELISA
a)Anti-OPXV IgG	Test to detect the presence of orthopox virus (OPXV) specific antibody
b)Anti-OPXV IgM	Test to detect the presence of OPXV antibodies
5)Virus-Host Interaction (Tissue tropism)	Test to detect the presence of OPXV antibody

**Table 6.** Treatment of Human monkeypox by Vaccines and antiviral drugs

Vaccines	Name	Features	Anti pox Virus
Second Generation	ACAM2000™	Second generation vaccine	MPOXV, Smallpox virus
Third Generation	IMVAMUNE	Third generation vaccine	MPOXV Smallpox virus
Antiviral drugs	Tecovirimat (ST-246)	Small molecule virus inhibitor	Cowpox virus, MPOXV Smallpox virus
	Brincidofovir (CMX001)	Viral DNA polymerase inhibitors	MPOXV
	Ribavirin and Tiazofurin	IMA dehydrogenase inhibitors	All poxviruses
	C-CA3-ADO, C3-NPC A	S adenosylhomocysteine hydrolase inhibitors	All poxviruses
	HPMA, Adenosine N1 oxide (ANO)	DNA polymerase inhibitor	All poxviruses
	Nioch-14	Nucleoside analogues inhibitor	MPOXV and vaccinia virus

18 years of age and older in high-risk populations. IMVAMUNE, in contrast to ACAM 2000, can be utilized by people with immunodeficiency disorders and atopic dermatitis<sup>44</sup>. MVA-BN, LC-16, or ACAM 2000 are the vaccines available for MPOX. However, only MVA and LC-16 are approved against MPOXV.<sup>42-45</sup>

**Antiviral drugs**

There are currently no antiviral medications specifically designed to cure MPOX, and interventions are primarily symptomatic and supportive. Drugs that fight the smallpox virus can be effective against MPOXV. Small molecule virus inhibitor tecovirimat (ST-246) possesses potent

anti-orthopoxvirus efficacy against the smallpox virus, MPOXV, and cowpox virus. By reducing the primary envelope protein's (F13L) ability to function, it can stop the propagation of the virus by preventing it from exiting an infected cell.<sup>46</sup> For the treatment of MPOX, it received approval in Europe in 2022.<sup>47</sup> Cidofovir and the Brincidofovir derivative (CMX001) work as viral DNA polymerase inhibitors. Cidofovir is an acyclic nucleoside phosphonate. The drug's lipid wrap breaks when CMX001 enters the host cells, releasing free Cidofovir that will then be phosphorylated into Cidofovir-diphosphate (CDV-PP). As a substitute matrix, CDV-PP prevents the production of viral DNA polymerase and finally prevents viral DNA synthesis at the DNA polymerase level.<sup>48</sup> In vitro and in vivo MPOXV replication inhibition is possible with Cidofovir and Brincidofovir.<sup>48,49</sup> Nioch-14 has potential as an anti-MPOXV medication because it is simple to make.<sup>50</sup> IMP inhibitors ribavirin and tiazofurin inhibit all poxviruses. Albeit variola virus (VARV) and MPOXV are more susceptible to their effects.<sup>49</sup> The DNA polymerase inhibitors HPMA, adenosine N1 oxide (ANO), and S-adenosylhomocysteine (SAH) hydrolase inhibitors C-CA3-ADO and C3-NPC all demonstrated intense anti-poxvirus activity and may employ as possible anti-MPOXV medications.<sup>51-53</sup>

## CONCLUSION

It suggests the prospect of long-term undetected transmission followed by recent amplification episodes, given the surprising spread of monkeypox across several non-endemic countries. Fortunately, some COVID-19 prevention techniques, including social disengagement, mask-wearing, surface sanitization, and hand washing, may also effectively stop the transmission of monkeypox. Due to vertical virus transmission from mother to fetus, monkeypox infection during pregnancy can increase the chance of prenatal loss. Preliminary findings indicate the necessity for broad maternal and fetal monitoring during pregnancies. A significant global registry of monkeypox infections in expecting women must be created to assess the true impact of this illness during pregnancy. International cooperation is crucial to containing the MPOX spread and lowering the threat posed by MPOX.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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None.

## DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

## ETHICS STATEMENT

Not applicable.

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