

## **Review Article**

### **Monkeypox and Monkey fever: Basic understanding for better community participation in disease control**

#### **Abstract**

Currently, Monkeypox is a threatening viral disease terminology around the world that worries the global community after the Coronavirus pandemic. Though many reports emerged in many countries recently, cases started appearing in India. Under these circumstances, public confusion is noticed between Monkeypox and Monkey fever across southern parts of India. Monkeypox and Monkey fever (Kyasanur Forest Disease) are categorized as potential emerging or reemerging Zoonotic diseases of humans and are fundamentally having clear-cut differentiation in their causative agent, clinical symptoms, and pathogenesis. Hence, it is a high priority to clarify and eliminate the unwanted confusions which would have tremendous and dangerous public health impacts. As defined by the Global Burden of Disease Study, Emerging Infections (EIs) are those that have recently appeared in a population or previously existed but are now gaining in prevalence or geographic spread rapidly. A disease emerges from the interactions between rapidly evolving infectious agents and the environmental changes and changes in human behavior that provide these agents with favorable ecological niches. This present communication attempts to clarify the fundamental differences between the two emerging infections—Monkeypox and Monkey fever which are affecting a significant group of the population worldwide. The communication is also trying to present a comparative picture of both the diseases towards developing adequate awareness among the public and expects to complement the community-based future control measures.

**Keywords:** Zoonotic diseases, Monkeypox, Monkey fever, Emerging, Reemerging

#### **Introduction**

The monkeypox virus (MPXV), is a viral zoonotic pathogen that causes typical illness among humans which are termed monkeypox (MPX). MPXV is categorized under the

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Orthopoxvirusgenus belonging to the Poxviridae family[1]. Monkeypox virus is similar to the virus causing smallpox, chickenpox, and cowpox of the same Orthopoxviridae[2]. On the other hand, Kyasanur Forest Disease (KFD) another popular terminology among public health authorities is an emerging virus zoonosis, is caused by the Kyasanur Forest Disease Virus (KFDV), which belongs to Flaviviridae[3].

Monkeypox virus is a brick-shaped virus enveloped with linear double-stranded DNA of around 197 kb size[4]. KFD virus is a positive-stranded RNA virus[5]that is nearly 11 kb in length [6]. According to the EU's "high threat" category of biodefence, MPXV falls under the "biosafety level 3"[7].KFDV is considered a highly pathogenic agent classified under BSL- 4[8]. As of 2017, KFDV has been classified with Risk Group 4 microorganisms in "Regulations and Guidelines on Biosafety of Recombinant DNA Research and Biocontainment."

A vesico-pustular lesion of an infected cynomolgus monkey was the first instance of Monkeypox being isolated in 1958 from Denmark and Zaire, then known as the Democratic Republic of Congo (DRC), first reported the disease in 1970 in a 9-month-old child[9]. The KFD virus was discovered in 1957 in the Kyasanur forest in Soraba, a place coming under the Shimoga district of Karnataka, India isolated from sick black-faced langurs[3].

An epidemic of human monkeypox has recently occurred in the African clime, where it has dominated for decades. Human monkeypox was first isolated in the western hemisphere in 2003[10].Due to the interaction between humans and monkeypox carrier animals,the disease is

spreading more rapidly followed by ecosystem degradation and a high rate of human-to-human transmission[10].

Kyasanur forest illness is known as "Monkey fever" because of its close association with monkey fatalities[11]. On the other hand, scientists came up with the name Monkeypox in 1958 after they first detected pox-like symptoms in colonies of monkeys kept for research in a laboratory. Researchers from thirty countries requested the name to be changed in a paper published on June 10 entitled "Urgent need for a nondiscriminatory and non-stigmatizing nomenclature for monkeypox virus". In their opinion, the current name doesn't comply with WHO guidelines that urge against using geographic areas and animal names during nomenclature[12]

### **Host and Transmission**

For Monkeypox, non-human primates, rodents, Gambian pouched rats, rope squirrels, dormice, and tree squirrels are found to be the most substantial reservoirs as they serve as a source of sustenance in some regions of the world[13] and humans are considered the incidental hosts[14] whereas in case of KFD, porcupines, rats, squirrels, mice, shrews, and cattle act as the reservoir host whereas Bonnet monkey with the red face (*Macaca radiata*) and Hanuman langur with black face (*Semnopithecus entellus*) is acting as the amplifying hosts, and humans are considered an accidental host[15]. Fig.1 schematically illustrate the comparison between the spread of Monkey fever and Monkeypox infection.

Infected reservoir creatures are the primary source of Monkeypox transmission. Saliva/respiratory excretions, lesion exudates, and crust residue are believed to be the primary sources of transmission. Viruses shed through feces could also be a transmission source[16]. Human-to-human transmission is possible for monkeypox through pus, skin lesions, and scabs or rashes. The transmission of monkeypox from person to person, including nosocomial and home transmission, is well reported[17]. There is no conclusive proof that seminal or vaginal fluids can transmit Monkeypox and fetal fatalities and vertical transmission have viruses reported in pregnant women[18].

KFDV is transmitted to humans either through tick bites (*Haemaphysalis spinigera*), which serve as reservoirs for the virus, or by coming into contact with a virus-infected animal especially ill or dead monkeys[5]. There have been no reports of transmission from one person to another

In the monkey pox population, mortality rates range from 0-11%, and kids and young individuals who have not been immunized against smallpox are at greater risk[19]. The highest deaths were reported among young children and HIV-positive patients[20]. Researchers found that the majority of monkeypox cases occurred among people under 40, and the average age of the affected people was around 31. The National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of High-Consequence Pathogens and Pathology (DHCPP), Centers for Disease Control and Prevention, states that in Africa, monkeypox causes the death of one in ten who contract it. KFD seems to be deadly with a case fatality of 3-10% every year[21][22].

### **Molecular characterization**

Molecular analysis revealed that the KFD virus' genome codes for a polyprotein that cleaves post-translationally to form three structural proteins (Envelope Glycoprotein M, Envelope Glycoprotein E, and Capsid protein) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5)[23]. The Envelope protein (E) of the KFD virus is a major causative element of tissue tropism among structural proteins[24]. This protein is accountable for facilitating the virus's entry into the host cell as well as for determining its immunogenetic and phenotypic characteristics, playing an important role in pathogenesis and immune evasion[25]. Monkeypox virus' terminals end contain Vaccinia Virus (VACV) homologs that are primarily involved in immunomodulation, and most have been found to affect pathogenicity and host range determination[4]. Its pathogenesis is essentially the same as smallpox, with the exception that tiny lesions on the skin or oral mucous membranes are most often the entry point for the virus from wildlife sources. Viral entry via the respiratory tract is also possible in rare cases of person-to-person transmission.

Monkeypox and smallpox viruses replicate in lymphoid tissue, but only MPXV causes swelling of lymph nodes. The virus first appears in MNP (mononuclear phagocyte) cells, then spreads through the bloodstream before reappearing in skin cells. KFDV's pathophysiology isn't totally understood. KFDV is reproduced largely in the brain, according to research employing mice models[26]. Other studies have gone further, describing the neurological alterations that occur in diseased species. Scientists revealed that KFDV causes multiplication of glial cells in the infested areas of the central nervous system, inflammation, and necrosis in the brain of KFDV-

infected mice. They suggested that KFDV is predominantly a neuropathic disorder with secondary symptoms caused by this aetiology.

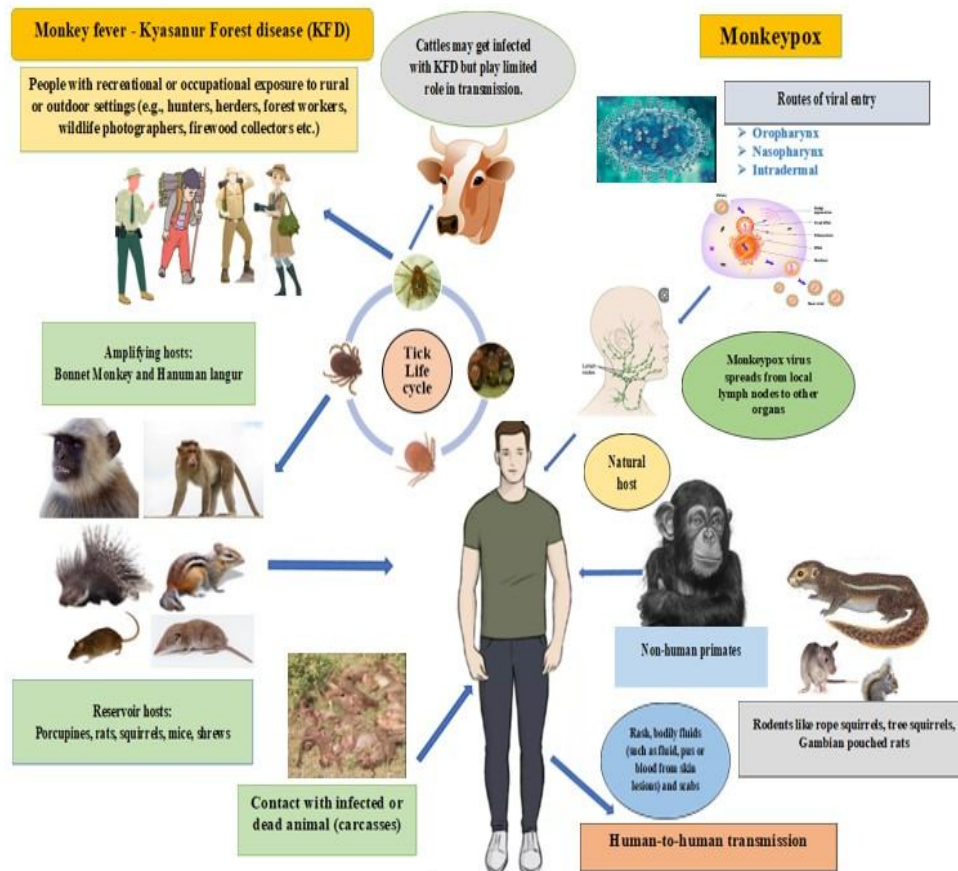


Fig 1: Schematic illustration comparing the spread of Monkey fever and Monkeypox infection

## Epidemiology

Since the first human case was discovered in 1970, the incidence of monkeypox has increased, with high prevalence in Nigeria, the Democratic Republic of the Congo, Cameroon, Liberia,

Sudan, Sierra Leone, Gabon, and the Central African Republic[27]. In neoteric years, the disease's swift emergence in countries such as the United States, United Kingdom, Singapore, and Israel, and the incidence has been linked to African origin[28][29]. Travelers play a vital role in spreading Monkeypox infections in new regions globally.

According to CDC National Centre for Emerging Zoonotic Diseases, around 400-500 positive cases of KFD are documented every year among the human population across India.

KFD was first reported in the Shimoga district of Karnataka, a primitive verdant territory in India's Western Ghats. The incidence of this disease was also reported in other districts of Karnataka, including Uttara Kannada, Chikkamagalore, Udupi, and Dakshina Kannada as well as Chamarajanagar and Belagavi (2016).

KFDV was discovered in monkey autopsies from Tamil Nadu's Nilgiris district in 2013. The serological evidence for KFD was detected among humans in other parts of India, namely Gujarat (Kutch and Saurashtra), West Bengal, Goa (North Goa District 2015) Maharashtra (Sindhudurg 2016)[30] and Kerala's Wayanad (2013) and Malappuram (2014)[31].

The smallpox vaccine given to the people before 1980 seemed to protect against the monkeypox virus also[32]. Cross-protective immunity has dwindled since the smallpox immunization campaign was ended[19] and as a result, the younger age group has become more susceptible to infection. However, a younger, non-immune generation coupled with the rise of hunting-dependent populations has resulted in the re-emergence of monkeypox.

## Environmental factors influencing the emergence of Infection

According to the studies done, it's been stated that environmental factors play a vital role in the survival of the Monkeypox virus[33] and also the spread of the KFD virus. There is a risk that climate change could alter the geographical distribution and seasonal patterns of infectious diseases, whether directly by altering the pathogen ranges or indirectly by altering vector and reservoir populations[33]. The increased interaction between humans and the virus's reservoir hosts has resulted in a greater re-emergence of infection. People moving into previously uncultivated areas increase the risk of cross-species infection as they come into contact with wild fauna and their livestock[34]. Farming, hunting, deforestation, camping, and other modes of habitat destruction have areas created a new avenue for infectious agents for invading humans[35]. The other reasons for the spreading of these viruses include climate change, demographic changes, population movement, civil wars, deforestation, rainforest exploitation, etc.[36]. Various studies have shown that temperature and light conditions affect the duration the monkeypox virus endures outside a host[33]. As a result of global warming, we can expect more severe rainfalls, droughts, and floods due to the disruption of the hydrologic cycle, contributing to the emergence of infectious diseases. Example is in the 2005 Sudan floods and subsequent monkeypox outbreaks. Due to the expansion of vector populations, food shortages, and effluents introduced in large water resources, the emergence of infectious diseases will be facilitated by these unique environmental conditions. In many places of the world, natural disasters have boosted migration between the states and this has led to the introduction of pathogens to newer

areas[37].The annihilation of natural forests has led to the relocation of animals to newer areas where the human population is there. Trekking causes people to go to deeper areas of the forest with their pet animals and becomes a carrier for these pathogens causing severe illness. KFD is mainly transmitted through ticks and the chance of domestic or other local animals transporting the tick to human settlements again could elevate the extent of the disease spread[38].Local residents who go to the forest to collect firewood are frequently infected by tick bites that carry and transmit the KFD virus. Mountaineers, hunters, trekkers, farmers, and charcoal makers in Karnataka and other southern states are at high risk of infection due to entertainment or work-related exposure to rural and outdoor settings [39].

### **Symptoms**

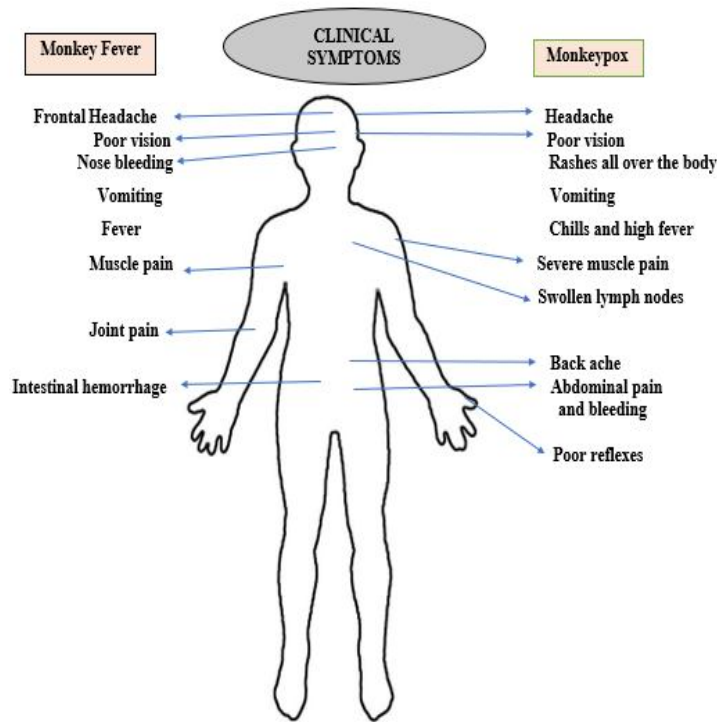
The incubation period of the Monkeypox virus differs from five to twenty-one days and the signs and symptoms experienced during this phase include fever, pharyngitis, rash, swelling of the lymph nodes, respiratory distress, secondary bacterial infection, bronchopneumonia, dehydration, sepsis, gastrointestinal involvement, encephalitis and infection of the cornea resulting in loss of vision[40].

The incubation period of the KFD virus is three to eightdays after the bite of an infective hard tick. KFD symptoms appear suddenly after the incubation period, with chills, fever, and headache. Three days after the initial symptom onset, vomiting, gastrointestinal symptoms, severe muscle pain, and bleeding problems may occur. Patients may have unusually low blood pressure as well as low platelet, white blood cell, and RBC counts. Some patients improve

without complications after one to two weeks of symptoms. However, at the beginning of the third week, a subset of patients (about 10 to 20 percent) experiences a subsequent upsurge of symptoms, indicating that the illness is biphasic with fever and brain-related issues. such as severe headaches, mental instabilities, shocks, and vision deficits are among the symptoms. For KFD, the estimated case-fatality rate ranges between 3 and 5%. The clinical spectrum begins with a sudden onset of fever, headache, chills, and generalized myalgia, particularly in the upper and lower back, neck, and extremities[41]. Fig.2 diagrammatically represents the symptoms and complications of KFD and Monkeypox infection .

**Table.1: Comparison between Monkey Fever and Monkeypox**

	<b>Monkey Fever</b>	<b>Monkeypox</b>
<b>First case reported</b>	Shimoga (Karnataka), India 1957	The Democratic Republic of Congo, 1970
<b>Causative Organism</b>	Kyasanur Forest Disease Virus (KFDV)	Monkeypox Virus (MPXV)
<b>Family</b>	<i>Flaviviridae</i>	<i>Poxviridae</i>
<b>Viral genome</b>	Positive single-stranded RNA	Double-stranded DNA
<b>Host</b>	<b>Reservoir host-</b> Porcupines, rats, squirrels, mice, shrews, and cattle <b>Amplifying host-</b> Red-faced Bonnet monkey ( <i>Macaca radiata</i> ) and Black-faced Hanuman langur ( <i>Semnopithecus entellus</i> ) <b>Accidental host-</b> Humans	<b>Reservoir host-</b> Non-human primates, rodents, Gambian pouched rats, rope squirrels, dormice, tree squirrels <b>Incidental host-</b> Humans
<b>Incubation period</b>	3-8 days	6-13 but can range from 5-21 days
<b>Mode of transmission</b>	Tick bite, Contact with infected animals.	Contact with infected animals/people through Saliva/respiratory excretions, lesion exudates, and crust residue
<b>Human to Human transmission</b>	Not yet reported	Possible cases are reported
<b>Symptoms</b>	Chills, fever, headache., vomiting, gastrointestinal symptoms, severe muscle pain, bleeding problems, generalized myalgia	Fever, pharyngitis, rash, swelling of the lymph nodes, respiratory distress, secondary bacterial infection, bronchopneumonia, dehydration, sepsis, gastrointestinal involvement, encephalitis, and infection of the cornea resulting in loss of vision
<b>Case Fatality</b>	3-6%	3-5%
<b>Treatment</b>	No specific treatment	Usually self-limited and the recovery occurs in 2-4 weeks. Can be managed by commonly available antiviral drugs.
<b>Vaccine</b>	Chick embryo fibroblast formalin inactivated vaccine.	Smallpox vaccination provides around 80% protection against MPXV.



**Fig: 2 Diagrammatic representation of symptoms and complications of Kyasanur forest disease (KFD- Monkey fever) and Monkeypox infection**

### Diagnosis

Once the patient exhibits any of the following symptoms, such as high-grade fever: Headache, Extreme Weakness, Myalgia, Nausea, Prostration, Diarrhea, Vomiting, or other symptoms like neurological or hemorrhagic complications, KFD is validated by detecting KFDV-specific viral RNA in blood or tissues using RT-PCR ( Reverse Transcription Polymerase Chain Reaction ) or real-time RT-PCR or by isolating KFDV from blood or tissues in a mouse model or cell culture

and by KFD Enzyme-Linked Immunosorbent Assay (ELISA) positive for immunoglobulin M (IgM)[42].

The samples from Monkeypox suspected cases should be collected from the skin lesions such as vesicles, dry crusts, and pustules. Skin biopsy is also done to collect the samples. The virus is visualized through a Transmission Electron Microscope and confirmed by PCR and ELISA, tissue culture, and immunofluorescence assay[43]

### **Vaccine and Treatment**

KFD does not have a specific treatment, however, early hospitalization and supportive therapy are critical. Proper intake of fluids and taking normal precautionary measures for patients with bleeding disorders are all part of supportive care. Monkeypox is usually self-limited and the recovery occurs in 2-4 weeks. According to the Centers for Disease Control and Prevention, monkeypox infection can be managed using the smallpox vaccine, ST-246(Tecovirimat), cidofovir, and Vaccinia Immune Globulin (VIG)[40].

A number of drugs are known to inhibit monkeypox virus replication includingbrincidofovir, tecovirimat, and intravenous vaccinia immune globulin. However, their efficacy against the monkeypox virus is unknown[44]. Scientific data reveals that the smallpox vaccination offers more than 80% protection from Monkeypox infection[45]. JYNNEOSTM vaccine (also known as Imvanex or Imvamune), has been licensed in the US to prevent monkeypox and smallpox[46].

Formalin inactivated chick embryo fibroblast is used as a vaccine against the Kyasanur Forest Disease Virus for use in KFD endemic areas for people 6 to 65 years of age. Multiple doses of the vaccine are required, and two doses are given to those aged 6 to 65 years at one-month intervals. Since the vaccine only provides temporary immunity, booster doses should be given 6-months after the primary vaccination and every five years after the last confirmed case in the area[47].

## **Conclusion**

Monkeypox and monkey fever are two distinct zoonotic infections caused by viruses of Orthopox and Flavivirus family respectively. The overall comparison between Monkeypox and Monkey fever is given Table.1 If you have traveled to monkeypox endemic countries like Liberia, Nigeria, DRC, etc., or had contact with those who have traveled, and if you have symptoms like a high fever, rashes, swollen lymph nodes, body ache, etc., you should get tested for monkeypox virus. Due in part to the skin lesions it creates, monkeypox rarely goes unreported when it infects a person, in contrast to Monkey fever. It would be quite concerning if monkeypox could spread asymptotically as it would make the virus more difficult to detect. Air travel turns the world into a global village in terms of infectious disease because "microbial traffic" follows the human host. As a result, diseases that were long thought to be exotic or tropical are now having a greater influence on the developed world[37]. The present worldwide outbreak of monkeypox virus infection in humans suggests changes in the biological characteristics of the virus, changes in human behavior, or both. Such changes may be triggered by diminishing

smallpox immunity, loosening coronavirus disease 2019 (Covid-19) preventative measures, resuming international travel, and sexual encounters associated with huge gatherings[48]. In the current scenario, people especially in South India need not worry and get confused about KFD (monkey fever) as the onset season is from September to August and the highest number of cases were always reported from February to April with a peak during March[49]. The increase in cases was associated with improved surveillance and high exposure to the forest due to scanty rainfall. KFD is mostly reported in the dry season when tourists travel to these forest areas for trekking, camping, and other adventurous activity. Hence, we can conclude that the factors like population demographics, climate change, deforestation, pollution, disturbance in the hydrological cycle, etc. influence the emergence and re-emergence of zoonotic viral infections. As per the available published information and data, we can conclude that the spreading of monkeypox can be controlled by the re-establishment of smallpox immunization to the current population or with any newly developed, regulatory-approved vaccines. Also, the spread of the KFD virus needs to be monitored properly since it is currently declared only as a viral disease endemic to some parts of India but chances are more to be declared a pandemic if spread across the borders of the country. The world must act swiftly and together to fill knowledge gaps and stop the pandemic. Rapid case identification is essential to containment in the absence of readily accessible prophylaxis or treatment. There are various ways that illnesses might present, as is typical in clinical medicine, and monkeypox or monkey fever is no exception. There is a need for targeted health promotion that sensitively encourages improved

screening and instruction in vulnerable populations. To accomplish a healthy community, the collaborative efforts of multiple disciplines at the local, national, and international levels to achieve people, animals, and the environment's optimal health[50] must be focused on as the health of animals and the environment we share is closely intertwined[51].

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