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Kyasanur Forest Disease: Re-alarming Illness in Western Ghats of India

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ABSTRACT: A highly infectious tick-borne virus is causing Kyasanur Forest Disease (KFD), which has been spreading in India in recent decades. Kyasanur Forest Disease (KFD) or Monkey fever is an emerging zoonotic viral tick borne disease affecting mainly monkeys. It causes severe febrile illness in humans, and was first recognized in Kyasanur Forest in 1957 associated with a high number of deaths among monkeys. Since then, between 400 and 500 human cases have been recorded annually. The monkeys and small mammals are common hosts of this virus. It is caused by the Flaviviridae family KFD virus (KFDV), and is transmitted by *Haemaphysalis* ticks to monkeys and humans. In the transmission of KFDV, humans act as a dead end-host, with no sufficient viremia for further transmission. A formalin-inactivated tissue culture vaccine is available for prophylaxis. Although the available vaccine once successfully controlled the KFD, the increasing trend of the disease over the last five years is alarming, regardless of routine vaccination. In this paper, a comprehensive endeavour has been made to review the Kyasanur forest disease. This review seeks to raise awareness of this alarming disease so that individuals with KFD are identified and provided with appropriate care.

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INTRODUCTION:

In April 2020, reports in The Hindu (Daily Newspaper) of an on-going outbreak of Kyasanur forest disease (KFD) in Shimoga district of Karnataka, India, the total number of 197 positive cases of KFD were seen in Karnataka since the beginning of the year. These reports serve as a reminder that KFD is a major public health issue in the region and that outbreaks occur at some

frequency. Although KFD frequently occurs in its endemic area, relatively little is known of its pathogenic mechanisms or the response of the host to infection.

Across the globe, ticks are important arthropod vectors for the transmission of several infectious agents and are responsible for causing diseases of humans and animals [1]. There are approximately 896 species of ticks from three families: *Argasidae* or soft ticks (193 species), *Ixodidae* or hard ticks (702 species), and *Nuttalliellidae* (represented by a monotypic species) [2]. Four major tick-borne diseases reported in India are Crimean-Congo haemorrhagic fever (CCHF), Indian tick typhus (ITT) and Kyasanur forest disease (KFD) and Ganjam. Among these, KFD is one of the major tick-borne viral haemorrhagic fevers that affects both monkeys and humans.

Kyasanur Forest Disease (KFD) or Monkey fever, a rare viral disease that has been found to be associated with the Russian Spring-Summer Virus but differs only in its haemorrhagic form. The virus belongs to the Flaviviridae family, genus flavivirus, and is classified as a Class IV biosafety pathogen [3]. In South India, many human cases report morbidity rates of around 2 to 10 % each year [4,5]. KFDV was first identified and isolated from sick and dead monkeys in Shimoga district forest regions located in Karnataka State, India, and reported in 1957 [6]. Infections of KFD were noted among people who visited the forests. The aim of this article is to examine KFD 's history and highlight the importance of the disease and others linked to flavivirus.

EPIDEMIOLOGY:

Kyasanur forest disease is also known as Monkey fever (Manga-na-kayale, in the Kannada language) because of its close association with monkey deaths. Kyasanur forest disease virus (KFDV) was first isolated in March 1957 from black-faced Hanuman langur monkey (*Semnopithecus entellus*) in Soraba Taluk of Shimoga district of Karnataka, India [7]. ICM's Virus Research Centre investigated and described Kyasanur forest disease as an illness similar to Russian spring-summer viral etiology. KFD is known for its unique existence in five districts - Shimoga, Chikmaglur, Uttar Kannada, Dakshina Kannada, and Udupi of Karnataka state. KFD was believed to be endemic in Shimoga District for a long time. The studies suggest that KFD virus or related viruses are present in other areas of India, which include Gujarat state, forested regions west of Kolkata, West Bengal state, and the Andaman Islands [8,9]. The epidemic period starts in November or December and peaks from January to April [10]. A total of 3263 human cases were reported in the state of Karnataka, of which 823 were confirmed in the laboratory and 28 deaths from 2003 to 2012. Every year outbreaks and several sporadic cases in Shimoga and neighbouring districts were reported with a case fatality rate of 3 to 4 % [11-14]. KFD outbreak was reported among the forest workers at the Bandipur Tiger Reserve in Chamarajanagar from 2012 to 2013. The virus was detected in ticks and/or monkeys at Nilgiri and Wayanad during the same period [15,16]. KFD outbreaks were specifically observed during 2014 and 2015 in new regions of Kerala's Wayanad and Malappuram districts [17]. KFD activity has also been reported recently in Goa, India [18]. Several cases are reported each year during the cashew nut harvesting season, which coincides with the seasonality of KFD in the Goa and Maharashtra Taluks in Sattari and Dodamarg. The major outbreaks since 2000 have been given in Table 1.

Table 1: Number of KFD confirmed human cases and deaths from 2000 to 2019.

Year	Number of Human KFD cases	Death
2000	130	9
2001	435	0
2002	98	6
2003	953	11
2004	153	5
2005	63	7
2007-2008	50	0
2009-2010	64	1
2011-2012	61	2
2013-2014	106	0
2014-2015	100	3
2015-2016	256	1
2016-2017	244	2
2017-2018	121	4
2018-2019	142	0

MODE OF TRANSMISSION:

KFD is often fatal among non-human primates and is known to affect two species of South Indian origin; *Macaca radiata* (*Bonnet macaque*) and langurs (e.g., *Gray langur*) in the genus Semnopithecus [19]. The principal vector involved in KFD is *Haemaphysalis spinigera* (Family: *Ixodidae*). KFDV has also been isolated from 16 different types of ticks, other than *Haemaphysalis spinigera* (Table 2).

Transmission occurs through the bite of infected hard ticks or through direct contact with infected or dead animals. KFDV is transmitted to other ticks that feed on the infected animals after infection. The species *Haemaphysalis* are the ticks of the temperate region and act as ectoparasites for more than one animal during its life cycle [20].

Table 2. List of ticks associated with Kyasanur forest disease transmission in India.

Ticks isolated with KFD in field condition	Ticks demonstrated with KFD in Laboratory
Haemaphysalis spinigera *Haemaphysalis turturis* *Haemaphysalis papuana kinneari* *Haemaphysalis minuta* *Haemaphysalis cuspidata* *Haemaphysalis kyasanurensis* *Haemaphysalis bispinosa* *Haemaphysalis wellingtoni* *Haemaphysalis aculeata* *Ixodes petauristae*	*Rhipicephalus haemaphysaloides* *Hyalomma marginatum issaci* *Ornithodoros crosi* *Argas persicus* *Dermacentor auratus* *Ixodes ceylonensis*

A *Haemaphysalis* tick life cycle includes three life stages (Larvae, Nymph and Adult) and feeds on three separate vertebrate hosts, needing blood supply either to pass into the next stage of life or to feed their eggs (Fig 1). Ticks normally inject their saliva into the host at the bite site, and the virus reaches the host with saliva. Tick bite and attachment when feeding on the host are usually painless and extend their vector capacity for longer periods (some hours to sometimes days). *Haemaphysalis* ticks can be contagious only after they are infected during their immature stage of life (usually larval period) and can become infectious by transstadial transmission for the rest of their lives. Nymphs are KFD's most contagious stage of life for both primates and humans because their host preferences are lowest in this stage. In Karnataka state, nymph activity from November to May is very high, correlating with a higher KFD transmission rate at this time of year. The immature ones are non-specific in host selection relative to adult ticks and often end up feeding on all immediately available living-hosts, including humans. Adult fed female ticks lay eggs below the leaves, which hatch to larvae. These also infest small rodents and monkeys and incidentally infest People, and they feed on their hosts. They then mature to nymphs, and the cycle is repeated. Nymphs and adults also spread the disease by a bite to rodents and rabbits, and this cycle of rodent-ticks goes on for more than one life-cycle [22].

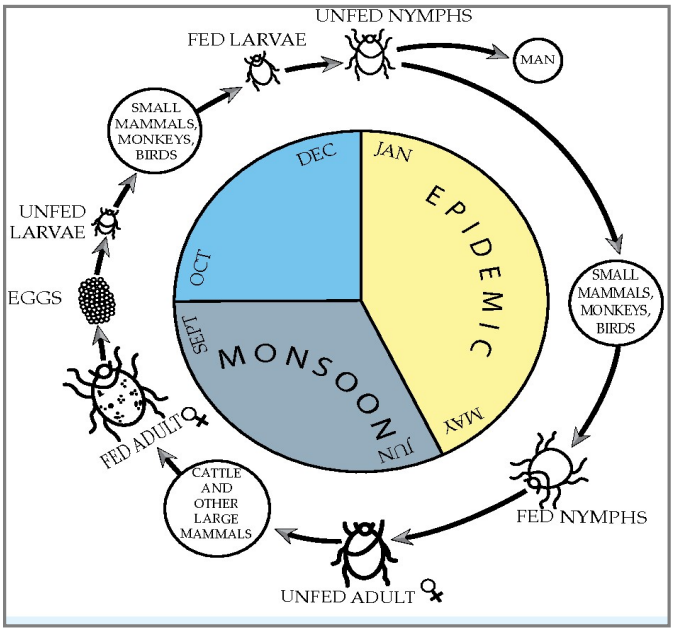

Fig 1. Life cycle of KFDV vector tick, *Haemaphysalis spinigera*.

Another mode of transmission-the most probable and efficient route for KFDV transmission-is through the co-feeding of ticks on a mammal (host) that allows viral transmission between ticks without host infection [23]. Fig 2 shows a wide variety of KFDV hosts, including humans, tick species, rodents (forest rats, shrews, white-bellied rats and white-tailed rabbits), bats, squirrels, ground-dwelling birds, Indian crested porcupines and monkeys (black-faced langur, macaque bonnet, and Gray langur). Changes in human-intrusive ecosystems may direct a mode of transmission of KFDV from wild animals to humans [24]. After a tick bite or contact with an infected animal, most notably a sick or recently dead monkey, transmission to humans can happen. No transmission between person and person has been described.

RISK OF EXPOSURE AND RISK GROUPS:

The KFD has been found widespread in various parts of Karnataka, Tamil Nadu and Kerala districts. Additionally, the associated KFDV has been isolated from Saudi Arabia and China. The Western Ghats provide ideal topographical and climatic conditions for vector ticks, making these Ghats the epitome of this tick-borne illness. The disease has a seasonal occurrence mainly during dry periods (November – June). The spill-over of this zoonotic disease occurs at the crossroads of animal-human-interaction, especially villages adjacent to

forest areas and inter-state frontiers. People who frequently visit Western Ghats forest areas such as firewood collectors, forest guards and officials, forest watchers, shepherds, travelers who camp in the forest areas, tribal community, cashew nut workers etc. are at higher risk of acquiring the illness. The movement of monkeys and rodents also contributes because they carry vector ticks that keep the KFD virus in nature through transovarial and trans-stadial transmission [19,25].

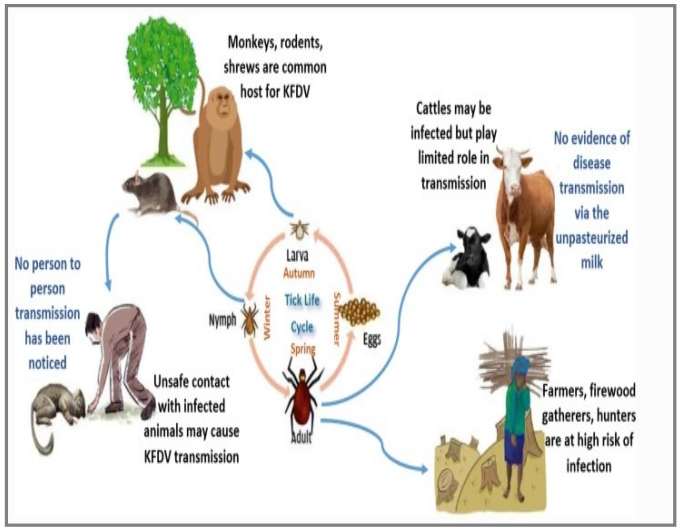

Fig 2. Mode of Transmission of Kyasanur Forest Disease.

PATHOGENESIS:

The interplay of various pathological mechanisms leading to this multisystemic disease in monkeys and humans is complicated and uncertain due to the lack of adequate *in vivo* and *in vitro* KFD models. Hypothesized pathogenesis elucidation of KFDV infection was presented in this section on the basis of published knowledge of KFDV immunopathology and closely related tick-borne flavivirus and haemorrhagic fever viruses (Fig 3).

KFDV is likely to be transmitted to a vertebrate host either by contact with an infected animal or through a tick bite that injects the virus and saliva components into the feeding skin site [26].

Proposed pathogenesis model of Kyasanur Forest Disease: Virus reaches (1) the body by bite of the tick or by contact with an infected animal. Virus initially targets the macrophages and dendritic cells. Virus multiplication (2) in these host cells results in high viremia, resulting in systemic dissemination of the virus to the spleen, liver and other replication sites to produce the disease's symptoms . The infected cells presenting antigen (APCs), which present T cells with viral antigens, could release massive volumes of pro-inflammatory cytokines early after infection, and also modulate the host immune response (3) through interferon production of type 1. Also, positive (activated) antigen T cells could produce IFN-1. The subsequent JAK-STAT signalling activation induces an antiviral state to alleviate the virus burden. Humoral immune response by activated B cells through the production of antibodies could also help to clear the body from the virus. To counteract the host immune response, KFDV employs its non-structural NS5 protein to antagonize IFN response (4) by inhibiting JAK-STAT pathway, potentially causing uncontrolled viral replication and poor immune response. Multi-systemic disease may be attributed to the pro-inflammatory cytokine storm that could contribute to immunosuppression and progression of the disease (5) by inducing disseminated intravascular coagulation (DIC), neurological complications, and vascular dysfunction leading to haemorrhagic manifestations, multi-organ failure, and shock [27,28]. Thus, the final balance between immune response and immunopathology therefore significantly governs the implications of viral infection and the severity of diseases [29].

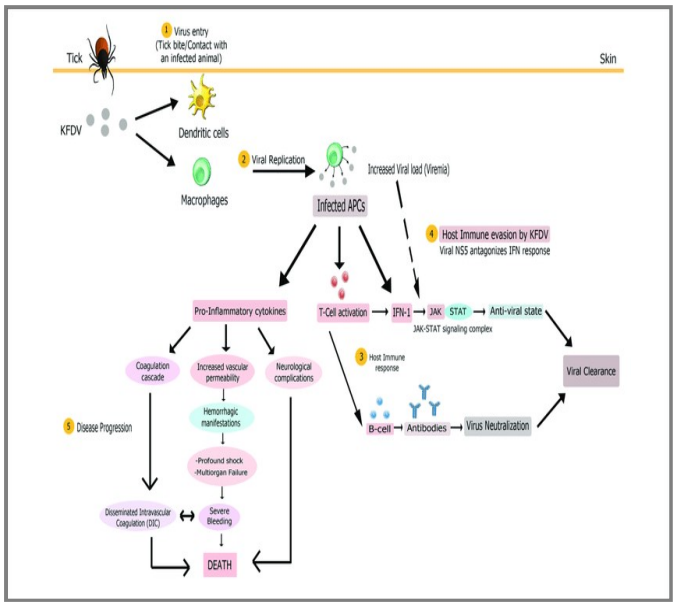

Fig 3. Proposed pathogenesis model of Kyasanur Forest Disease.

CLINICAL SIGNS AND SYMPTOMS:

In humans, KFD is estimated to have an incubation period of around 3 to 8 days after tick bites or exposure. It is followed by an abrupt onset of disease lasting approximately 1 to 2 weeks. This febrile period includes

clinical symptoms such as sudden chills, frontal headache, vomiting, diarrhoea, sore throat, high fever (104 °F), generalized muscle pain and a severe degree of prostration, gastrointestinal disturbances, insomnia, sore throat, decreased blood pressure and heart rate, pain in muscles, extremities and Ophthalmic presentation of this disease includes haemorrhages in the conjunctiva, vitreous humour, and retina, mild iritis, the opacity of lens and keratitis.

Haemorrhagic manifestations such as epistaxis, haemoptysis, bleeding from the gums and gastrointestinal bleeding are observed during this viraemic phase. Haematemesis or the appearance of fresh blood in the stool may also be observed [24,29,30]. Patients may also experience abnormally low blood pressure, and low platelet, red blood cell, and white blood cell count. A very constant feature is papulovesicular lesions' appearance on the soft palate, but no skin eruption has been noted [31].

Some patients recuperate without complication after 1 to 2 weeks of symptoms. However, the disease is biphasic for a subset of patients (10 to 20 %) who experience a second wave of symptoms at the start of the third week. This second non viraemic phase is characterized by the same symptoms observed in the first phase along with neurological complications, severe headache, mental disturbances, tremors, and vision deficits, lasting for about 2 to 12 days.

The convalescent phase of the disease is prolonged (Table 3). In the convalescent period, occasional tremors, body weakness is seen in survivors extending up to a month. The case fatality rate is approximately 3 to 5 % [31,32]. In naive non-endemic areas, higher fatality is reported, largely due to lack of awareness and also lower herd immunity to the virus [15,19,31,32].

DIAGNOSIS:

Early diagnosis of KFD is better than late diagnosis because viremia increases to 3 CFU/ml within a couple of days of infection and remains high for up to 2 weeks. Precise and rapid differential diagnostic testing should be established to diagnose and confirm KFD because the clinical signs of KFD are indistinguishable from various other haemorrhagic / viral fevers. Other illnesses like influenza, typhoid, and rickettsia fevers should be diagnosed differently from KFD [33]. Earlier for detection of KFD, virus isolation and some methods of detection based on antibodies, such as hemagglutination inhibition (HI), complement fixation (CF) and neutralization test (NT) were used. With the advancement in technology, Laboratories developed diverse molecular diagnostic methods for the diagnosis of KFD. Samples of blood and serum should be collected aseptically from patients with necessary protective measures for the collection of samples by the personnel. Complete blood photo analysis of suspected patients should be performed in blood samples. Also, different tests for liver and kidney functioning.

Table 3. Clinical course of Kyasanur Forest Disease.

Clinical Course	Period	Signs and Symptoms
First Phase	7-12 days post incubation period	Sudden onset of continuous high grade fever, diarrhoea, vomiting, severe prostration, myalgia, headache.
Second Phase (Occurs in a subset of 10 to 20 % of the cases)	2-12 days after an afebrile period of 1-2 weeks	Meningeal signs, altered sensorium, seizure, bleeding manifestations, and prolonged convalescent period (may last for a few months)

DIFFERENTIAL DIAGNOSIS:

Different molecular tests such as real-time RT-PCR, IgG, and IgM capture ELISA [MAC-ELISA] have been developed in the BSL-3 lab for the detection and understanding of KFD throughout the acute stage of infection [30-34].

Serological Methods:

KFDV antibodies from many Indian states, especially from south-western states like Gujarat and Maharashtra, also from western Bengal and Andaman and the Nicobar Islands, were demonstrated by HI test and neutralization test. Laboratory diagnosis of the disease is made by molecular tests, while IgM and IgG antibodies are detectable after the fifth day by indirect immunofluorescence test or ELISA. KFD IgM antibodies were determined by enzyme-linked immunosorbent assay (ELISA). KFD IgM antibody can be detected from the fifth day of onset of symptoms till three months.

Virus Isolation

KFDV virus isolation can be done in cell lines BHK 21, Vero E6, embryonic chick cells or in mice. KFDV will produce its characteristic cytopathic effect in BHK 21.

Intra-cerebral inoculation of the virus in 3 day old mice will in all cause death. Similar findings were obtained in 50 day old mice following intra-peritoneal inoculation.

Molecular Diagnosis:

Detection of KFDV by real-time RT-PCR and RT-PCR. They are the first check row for KFD diagnosis. Real-time RT-PCR for rapid diagnosis of CCHFV infections is the test of choice in the acute phase, and for ticks. The RT–PCR reactions are highly specific and sensitive compared to other conventional methods. The flaviviruses specific NS–5 region was targeted for primer designing. The present real-time assay is very sensitive and nearly as sensitive as detecting up to 10 copies of viral RNA. This analysis assist in diagnosis of the diseases.

TREATMENT:

There is currently no effective antiviral treatment for KFDV in humans; early hospitalization and supportive care are becoming increasingly essential. Yet timely symptomatic and supportive treatment involving hydration maintenance, hemodynamic stabilization and neurological symptom management reduces morbidity and mortality [35].

PREVENTION AND CONTROL:

Tick-borne diseases are emerging due to changes in public health policy, resistance to acaricides, climate change and the emergence of new pathogen variants. Measures to reverse these same conditions need to be taken. Prevention strategies such as quarantine, vaccination, early diagnosis, and tick control will limit the virus' entry into new areas. The KFDV has been listed as pathogenic risk category IV. Vaccination is one of KFD 's key prevention techniques.

Other control strategies include Wearing protective clothing and tick protection when handling infectious materials. Access to infected forest areas during outbreak time is strictly prohibited. When visit is necessary, use protective clothing and gum boots to cover the entire body and apply some insect repellent to the portion of the exposed body. Integrated Pest/ Vector Management (IPM) could be a potential approach for tick control in the future.

KFD Vaccine:

An inactivated/ killed tissue culture vaccine has been used in endemic areas of Karnataka, India, since 1990. In general, the antibodies produced against viral infections are retained at high rates for years due to repeated re-exposure to the virus in the form of subclinical infections or exposure to closely related viruses. As with other arboviruses, HI and complement fixing (CF) antibodies start to rise in the first week after KFD starts. During the second week, the neutralizing antibodies appear and the titers hit the peak at 3rd to 4th week.

Also, in the absence of re-exposure, antibody- mediated immunity to KFDV continues for a decade [36].

The very first vaccine tested in the early 1960s to manage KFD in Shimoga District, Mysore State of India, was a 5 to 10 % suspension of formalin-inactivated RSSE virus (mouse brain preparation) produced by Walter Reed Army Research Laboratory, Washington, United States. The vaccine induced a weak HI antibody response but did not stimulate an antibody with CF response. In many individuals with previous KFDV infection, the vaccine failed to evoke a booster response. Therefore, the RSSE vaccine was found to be ineffective in reducing the KFD attack rate or altering the course of the disease [36,37].

The first attempt to develop KFDV was subsequently made (in 1965) by growing KFDV in infant Swiss albino mice's brains and subsequent inactivation by formalin. An experimental KFDV vaccine was also developed by the growth of the virus in the embryo of chicks, but the product was poorly immunogenic and did not elicit a neutralizing response in mice [38,39]. Later in the year 1966, Formalin-inactivated chick embryo fibroblast cell culture based vaccine was prepared at the Institute of Animal Health & Veterinary Biologicals (IAH & VB), Hebbal, Bengaluru, Department of Health & Family Welfare, Government of Karnataka, India. The vaccine was found to be immunogenic, potent, stable and safe. The vaccine is currently in use in the endemic areas in Karnataka state of India [40]. Coverage of vaccines is fairly good.

The local government authorities are routinely vaccinating almost all the individuals including children. Vaccination is required in multiple doses. Two doses of the vaccine are administered at an interval of one month for individuals aged 7 to 65 years. Since the immunity conferred by the vaccination is short-lived, booster doses are recommended within 6 to 9 months after primary vaccination and repeated after the last confirmed case in the area for five consecutive years. The KFDV vaccine consists of formalin-inactivated KFDV. The vaccine has an efficacy rate of 62.4 % for people who receive two doses. In a study conducted by Kasabi, *et al*. (2013)

noticed low coverage of vaccines in affected areas even less than half of the target population and the efficiency of the vaccines was around 62 % in individuals who received initial two doses and 83 % in individuals who received further boosters [41]. The current KFD vaccine does not completely protect against KFDV infection; among vaccinated individuals, viremic period is shorter compared to unvaccinated cases.

The increasing pattern of KFD cases in the state of Karnataka warrants the development of a new vaccine preparation, which includes currently circulating KFDV. Improper vaccine storage and lack of cold chain management result in vaccine inactivation and can be another reason for the rising KFD amid vaccination routine. Cattles have low susceptibility to KFDV and the antibody persists for a very long period of time (5 years). Therefore, cattle can be used as an indicator in field surveillance for determining KFDV 's past operation, but was not considered practicable.

CONCLUSION:

Kyasanur forest disease (KFD) or Monkey fever, is an emerging zoonotic viral tick borne disease. KFD is a historically understudied tick-borne disease in which every year, hundreds of human cases are reporting from South India. Given its geographical relevance, KFDV carries considerable importance in flavivirus formation, evolution, dispersal and antigenic diversity. KFDV 's ecology and epidemiology are unique, with distinct clinical symptoms and pathogenic manifestations. It is very important and necessary to study pathogenesis in depth, as it will pave the way for the development of better preventive and therapeutic approaches to counter KFD.

Although the available vaccine once successfully controlled the KFD, the increasing trend of the disease over the last five years is alarming, regardless of routine vaccination. More emphasis on molecular studies is needed to understand the mechanism of evolution of virulence in KFDV. Given the need to develop safer and more effective vaccines in general, efforts should be made to develop an alternative version of the KFD vaccine. Such efforts will go a long way towards developing more efficient KFD vaccines and disease control. There is a significant gap in our knowledge regarding KFD and urgent work and studies are needed to reduce the burden of monkey fever, so that sustainable interventions can be made and KFD mortality can be reduced [42].

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