

Kyasanur Forest Disease (KFD): Drawing Attention and Concern about its Current Status

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Abstract

Kyasanur Forest Disease (KFD) is a seasonal haemorrhagic viral fever observed in the region of Western Ghats of South India. It is an endemic caused by Kyasanur Forest Disease Virus with tick as its primary vector. Monkeys are the primary hosts whereas humans are the terminal hosts. Although, the disease was identified in 1957, it still continues to be neglected due to its restricted prevalence. There are limited diagnostic and therapeutic interventions available as the research studies require huge monetary support. The development and manufacture of vaccines for such diseases at an affordable price to cater the risk group who belong to the lower income strata, are the barriers faced in combating the disease. This mini review article sheds light on the history of KFD, factors involved in the spread of the disease and challenges faced in fighting the disease. Diagnostic methods, prophylactic interventions, current status and advancements made regarding the disease have been discussed. The role of various health institutes and research bodies in contributing towards increasing the knowledge about the disease has been highlighted.

Keywords: Kyasanur Forest Disease; Endemic; Ticks; Monkeys; Rare Disease

Abbreviations

KFD: Kyasanur Forest Disease; KFDV: Kyasanur Forest Disease Virus; AHF: Alkhurma Haemorrhagic Fever; AHFV: Alkhurma Haemorrhagic Fever Virus; RNA: Ribo Nucleic Acid; RT-PCR: Reverse Transcriptase- Polymerase Chain Reaction; ICMR: Indian Council of Medical Research; NIV: National Institute of Virology.

Introduction

Kyasanur Forest Disease, commonly known as KFD or monkey fever, is a zoonotic disease. It is caused by Kyasanur Forest Disease Virus, a single stranded RNA positive virus, which belongs to the family *Flaviviridae*. The disease was

first identified in 1957 during an outbreak among macaques in the Kyasanur forest in Shivamogga. It is endemic to forest regions of Western Ghats; commonly seen in Shivamogga, Chikkamagaluru, Uttara Kannada and Dakshina Kannada of Karnataka, India. Sometimes, the outbreaks are seen in Wayanad of Kerala, Nilgiris districts of Kerala and also in some parts of Maharashtra. The primary vectors of the disease are *Hemaphysalis spinigera* and *Hemaphysalis turturis*. These hard ticks act as host for the viral replication for its entire lifetime. Infected ticks transmit the virus to vulnerable hosts such as monkeys, shrews and rodents. Humans are the terminal hosts to get infected when bitten by tick nymphs or when they come in contact with sick or dead animals. KFDV transmission through domestic animals such as goat, cattle or sheep is rare. No human to human

transmission of KFDV is noted [1-3]. From the beginning of 2024, there has been a surge in Kyasanur Forest Disease (KFD) cases reported, which has drawn attention to the state of Karnataka. The disease raises concern as fatalities were

reported. It can be classified as a rare disease due to its very low incidence and prevalence. The details of recent reports are provided in Table 1.

S. No.	Date	Newspaper	Reference link
1.	9-Jan-24	Deccan Herald	https://www.deccanherald.com/india/karnataka/19-year-old-girl-dies-of-kyasanur-forest-disease-in-karnataka-2841214
2.	5-Feb-24	Times of India	https://timesofindia.indiatimes.com/city/bengaluru/latest-update-11-new-cases-of-kyasanur-forest-disease-in-shivamogga/articleshow/107411583.cms
3.	9-Feb-24	The Hindu	https://www.thehindu.com/sci-tech/health/kyasanur-forest-disease-the-assault-of-the-tick/article67822708.ece
4.	12-Feb-24	The New Indian Express	https://www.newindianexpress.com/states/tamil-nadu/2024/feb/12/tn-issues-advisory-as-53-kyasanur-forest-disease-cases-reported-in-karnataka
5.	25-Feb-24	Deccan Herald	https://www.deccanherald.com/india/karnataka/first-monkey-fever-case-reported-in-udupi-2909041
6.	27-Feb-24	The Hindu	https://www.thehindu.com/news/national/karnataka/woman-from-siddapura-taluk-dies-of-kfd-in-shivamogga-karnataka/article67887727.ece
7.	3-Mar-24	The Hindu	https://www.thehindu.com/news/national/karnataka/eight-more-cases-of-kfd-reported-on-march-2/article67909714.ece
8.	20-Mar-24	The Hindu	https://www.thehindu.com/news/national/karnataka/karnataka-seven-new-cases-of-kfd/article67972084.ece
9.	12-Apr-24	Mongabay-India	https://india.mongabay.com/2024/04/kyasanur-forest-disease-a-ticking-health-bomb-in-the-western-ghats/
10.	15-Apr-24	Scroll.in	https://scroll.in/article/1066569/kyasanur-forest-disease-a-tick-borne-viral-illness-is-spreading-in-the-western-ghats

Table 1: List of recent newspaper reports related to KFD.

Factors involved in Transmission of KFDV

The Western Ghats is a hub for various kinds of monkeys. The macaque species such as *Macaca silenus*, *Macaca radiata*, *Semnopithecus entellus* and *Trachypithecus johnii* are native to Western Ghats. They are the principal amplifying hosts when affected by the infected ticks. These animals significantly transmits the disease to humans by acting as a reservoir for the virus [3,4]. The presence of monkeys in high number makes them an important part of the ecosystem and their interaction with the fauna makes them highly vulnerable to viral infection. Seasonality and climate plays an important role in the occurrence of KFD. The outbreaks are commonly seen during the post-monsoon period. Studies have identified that the transmission period of KFD is between November and June. Decreased or insignificant precipitation during these months is the reason for disease transmission. Surprisingly, the monsoon season experienced from June to October are observed as non- transmission period.

Extensive breeding of ticks occur during rainy season. Hot and dry climatic conditions along with water stagnation, ambient temperature (18°C-30°C), moist soil and humid conditions are necessary for the growth and development of the ticks. During the post monsoon time, the nymphs are extremely active and attack monkeys and other hosts for blood meal and finally infect humans. Increased agricultural activities, deforestation and collection of wood and other forest products etc. expose humans to KFDV attack [5,6]. Hunters, farmers, wood cutters, forest workers are at high risk of acquiring the disease.

Challenges Faced in Fighting KFD

In spite of severe pathogenicity, KFD remains as a highly understudied disease. This section discusses several challenges and hindrances faced in effective prevention and control of KFD. KFD is a viral haemorrhagic fever which recurs every year and affects the lives of common people. The exposure of ticks to people dwelling in the forest and

surrounding areas is so common that the possible spread of the disease is heavily undermined [7]. Some challenges are listed below.

- Regular screening among the masses residing in the disease-prone areas is difficult due to environmental and geographical barriers.
- Extensive anthropogenic interference in the ecosystem, drastic climate change and dwindling wildlife population has contributed to the possible spread of disease [8].
- Although the causative agent and mode of transmission of disease has been identified, the pathogenesis of KFD is yet to be fully understood due to insufficient *in-vivo* and *in-vitro* models. There is a need for more research regarding molecular and genetic studies of the pathogen and interaction with the hosts.
- The low prevalence of the disease makes it difficult to attract the interest of private companies to conduct in-depth research studies have to be carried out regarding KFD for better characterization of the disease and develop desirable solutions.
- The vaccines which are developed are of substandard levels as their efficacy is limited. Even the vaccinated people are found to contract KFD. Thus vaccines have failed to confer protection against the disease. There is no complete treatment or effective prophylaxis to combat the disease due to unavailability of substantial data regarding clinical and epidemiological aspects of the disease.

Established Similarities between KFDV and AHFV

Alkhurma haemorrhagic fever virus is a pathogen which possesses high degree of similarity in comparison to KFDV. Both the viruses belong to the same family i.e. *Flaviviridae*. AHF is also a zoonotic disease which is spread by ticks belonging to *Hyalomma* species. It was first identified in Saudi Arabia. Patients affected by AHFV manifest similar signs and symptoms as that of KFD. The AHFV possesses about 97% sequence similarity as that of KFDV. Thus, the former virus is considered as subset of KFDV [9]. The laboratory concerned with these viruses should follow biosafety level-4 measures set by Centers for Disease Control and Prevention due to their severe virulence and lack of effective counter measures [10]. The complexity and variability of the viruses makes it difficult to design vaccine which could target specific parts of virus to elicit immune response against different strains of the virus. Currently, there is no specific antiviral treatment or effective vaccines to treat AHF.

Diagnostic Methods of KFD

The incubation period of the KFDV is about 3-8 days. The initial signs and symptoms of KFD are fever, headache,

chills and malaise. Severe myalgia, vomiting, diarrhoea, photophobia, tremors, visual defects, mental disturbances, gastrointestinal disorders along with intestinal bleeding are the symptoms developed in the patients as the severity of the infection increases. Studies have highlighted clinical features such as leucopenia, thrombocytopenia, low erythrocyte sedimentation rate, elevated levels of transaminases and albuminuria [11]. Molecular detection by polymerase chain reaction test or isolation of virus from blood can be conducted to diagnose the infection in humans, monkeys and ticks. Enzyme linked immunosorbent serologic assay is useful in detection of IgM antibody against KFDV in humans. Several novel diagnostic techniques are reported which are capable of diagnosing the viral infection. One-step reverse transcription loop-mediated isothermal amplification assay for molecular diagnosis of KFD was identified as an approach to examine clinical samples in resource limited regions of outbreaks [12]. A single step based novel isothermal reverse transcription polymerase spiral reaction assay using magnetic bead based viral RNA extraction could be explored for visual detection of KFDV [13]. Cutting-edge technologies provide an opportunity to detect virus using nanotechnology-based biosensors, lab-on-a-chip technology, digital PCR, microfluidic devices, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR-associated proteins) and NEXT-Generation Sequencing system etc.

Prophylaxis and Supportive Therapy

As of now, there is no specific drug prescribed to provide therapeutic action against KFD. Vaccines are available to provide immunity against the infection but their efficacy is limited and questionable. Symptomatic treatment and early hospitalization is of utmost importance. Preventive measures are to be followed to avoid the contraction of disease. Vector control programmes play an important role in reducing the vector's population. Acaricides are useful in controlling ticks and mites. Use of insect repellants (containing N, N-diethyl metatoluamide) and wearing protective clothes is advisable. Care must be taken to stop the excessive breeding of vectors by adopting measures to alter their habitat and destroy the insects during their larvae stage. Awareness must be spread among the health care workers regarding the disease.

The professionals must wear personal protective equipments to prevent any possible infection from infected animals or individuals. Better monitoring and surveillance systems are to be established to keep track of the spreading of infection among monkeys and people for early detection, risk assessment, understanding the dynamics of risk transmission and aid the research works. Supportive therapy is the only remedy to treat KFD as there is no specific antiviral treatment. A formalin-inactivated whole virus vaccine produced in chick-embryo fibroblasts was

used as a preventative measure against KFDV. The efficacy of this vaccine was questionable as it was unable to control the infection, despite administering multiple doses [14,15]. Fluid and electrolyte management and antiemetic therapy is of utmost need to treat the patient as there is excess loss of electrolytes, which is further aggravated by nausea and vomiting. The patient has to be isolated and quarantined to prevent the spread of infection and should be closely monitored for any complications.

Role of Various Research Bodies/ Institutions

Indian Council of Medical Research (ICMR), the apex medical research body in India, has set up Vector Borne Diseases Science Forum. It is a platform which focuses on identifying and prioritizing gap areas in the control of various vector-borne diseases [16]. It is also working on developing a new vaccine for KFD [17]. As per the ICMR Annual Report (2021-22), tick survey was conducted in Tamil Nadu to explore the spatial biodiversity of *Ixodidae* ticks. Mapping the potential risk areas of KFD was done in the states of Karnataka, Goa, and Maharashtra. National Institute of Virology, Pune has developed a nested RT-PCR (nRT-PCR) kit for diagnosis of KFDV in monkeys, ticks and humans. The test kit developed is user friendly, cost effective, specific and highly sensitive. It was developed using gene sequences of the NS-5/non-coding region [18]. Projects were conducted in 2022 to analyse the host immune responses in symptomatic and recovered cases of KFD. As per the ICMR Annual Report (2022-23), 18 laboratories were trained by NIV for diagnosis of KFD. Researchers from National Institute for Allergy and Infectious Diseases have been able to develop KFD vaccine based on based on the vesicular stomatitis virus- Ebola vaccine (VSV-EBOV) which also expresses the KFDV prn and E proteins [14,19].

Latest update on availability KFD Vaccine

From the article reported in The Hindu, Bengaluru, dated 17th October 2024, the Minister of Health and Family Welfare, Govt. of Karnataka has said that the KFD vaccine would be available for use by 2026. As per the report, since the earlier vaccine was ineffective, a new vaccine is being developed by Indian Immunologicals Ltd., Hyderabad with the concurrences of ICMR, has shown promising results for studies conducted on macaque monkey. Trials on humans would commence in April 2025 and the vaccine will be available in 2026.

Conclusion

Kyasanur Forest Disease, a rare illness observed in certain parts of South western forest region of India, has traditionally seen limited incidence with approximately 400-500 cases

reported annually. However, recent years have witnessed a notable increase in cases, with projections indicating a peak in 2024 [20]. To address this concerning trend, the Government of Karnataka, alongside premier medical institutions and research bodies associated with diseases, has been actively engaged in surveillance, prevention, and control measures for the disease. These efforts encompass raising public awareness through periodic issue of guidelines to public about the disease and ongoing endeavors to control the spread of infection as well as develop effective vaccines for prophylactic use, aiming to stem the disease's spread and mitigate its impact on affected communities [21,22].

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Conflict of Interest

None to declare

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