

Why has an Optimally Effective Vaccine for Kyasanur Forest Disease not yet been achieved? A Scientific, Biological, Immunological, Ecological, and Community-Level Perspective

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Abstract

The Kyasanur forest disease (KFD) is a tick-borne disease that is endemic to Western Ghats in India. There is a formalin-inactivated vaccine for KFD virus, but it has been difficult to find one that is consistently effective or durable. Many scientific and translational factors contribute to this problem. First, the cycle of zoonotic transmission is quite complex. Second, human exposure happens episodically. Third, there is considerable genetic variation among the circulating strains of the virus. Additionally, flavivirus-specific immunological challenges such as the requirement for balanced humoral and cellular immunity and the risks of antibody-dependent enhancement, make the use of traditional vaccination platforms difficult. KAP (knowledge-attitude-practice) studies indicate that variability in vaccine acceptance and community awareness of vaccine use and booster schedules seem to be significant factors affecting real-life efficacy of vaccines. Thus, the lack of an optimally effective KFD vaccine is due to multiple facets of the complexity of KFD, rather than a lack of effort. Reverse vaccinology, immuno-informatics, and community-engaged vaccine development approaches are promising avenues for developing next-generation KFD vaccines and represent the best path for long-term, sustainable control of KFD in today's world.

Keywords: Kyasanur Forest Disease, Vaccine, KAP, Zoonotic infection.

Introduction

Kyasanur Forest Disease (KFD) is one of the earliest diagnosed tick-borne viral hemorrhagic fevers in India and remains a geographically limited expanding zoonosis. Since it was first identified in the late 1950s, KFD continues to pose a threat to public health as KFD is a recurrent public health problem, especially among populations that live near forests and are in occupations that expose them to KFD. The disease has the following characteristics: (1) acute febrile illness; (2) hemorrhagic symptoms; and (3) occasional neurological symptoms; therefore, KFD causes significant morbidity among people living in endemic areas [1], [2].

The expansion of KFD along the Western Ghats demonstrates that KFD is an ecologically dynamic disease. Besides Karnataka, KFD has been reported as a human disease and

serological evidence of KFDV transmission in other states, such as Kerala, Goa, Maharashtra and Tamil Nadu (Figure:1). The expansion of KFD has followed predominantly through forested areas of the Western Ghats where ecological conditions are conducive to the continued survival of tick vectors and vertebrate reservoir hosts [3], [4].

In Karnataka, the disease burden associated with KFD continues to be the highest, with repeated outbreaks reported in the districts of Shivamogga, Uttara Kannada, Chikkamagaluru, and Dakshina Kannada. In Kerala, districts bordering Karnataka (i.e., Wayanad and Malappuram) have reported cases, and there are sporadic outbreaks and evidence of seropositive animals and/or humans indicating continued silent transmission of KFDV in Goa and Maharashtra [5].

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Reports from Tamil Nadu, especially from forested regions of the Nilgiris and adjoining districts, further underscore the southward expansion of the virus.

Prevalence and Serological evidence for KFD in India (1957-March 2024)

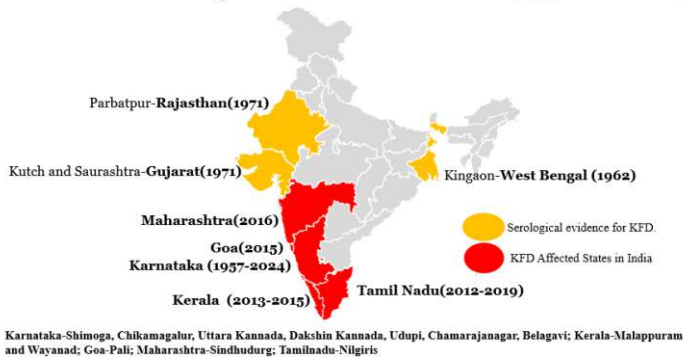


Figure 1: Indian map showing the prevalence of KFD across the Western Ghats and the States with Serological evidence for KFDV

The ecological and anthropogenic factors related to the expansion of KFD include deforestation, land use changes, increased human intrusion into forest ecosystems, livestock movement, and changes to tick/host interactions. For years, efforts to control KFD have been thwarted by the difficulty of obtaining effective antiviral treatments for KFD. Furthermore, most existing vaccines provide only short-term protection in populations that have had little or no prior exposure, creating increased risk of KFD outbreaks and increased morbidity from KFD infections.

Ecological Complexity and Zoonotic Transmission

A fundamental challenge in controlling KFD is due to the complexity of its zoonotic transmission cycle. KFDV is transmitted among *Haemaphysalis* ixodid ticks and several species of small mammals, including multiple non-human primate species; humans are considered incidental hosts; therefore, humans are not responsible for the prolonged transmission of KFDV, eliminating the opportunity to achieve herd immunity or interrupt KFDV transmission by merely implementing human-oriented intervention strategies [2], [6].

The episodic nature of KFD outbreaks (seasonal), along with the absence of symptomatic KFD cases during silent viral circulation within forest ecosystems, also creates significant limitations for surveillance systems and the development of reliable immune correlates of protection.

Immunological Issues in Developing Vaccines for KFD

The flavivirus family includes KFDV, which has its own unique set of immunological challenges. To achieve a protective immune response, there is a need for optimal levels of neutralizing antibodies and strong cell mediated (T cell) immunity, each of which contribute separately to the overall response against virus infection. Although neutralizing antibodies constitute a critical component of the immune response in flaviviruses as documented by research [7], [8],

flavivirus infections have also been associated with antibody-dependent enhancement (ADE), where sub-neutralizing levels of antibodies can lead to enhanced disease severity upon subsequent infection [9], [10].

The limited immunological studies in humans with KFD, inability to do human challenge studies, and a lack of knowledge relating to the durability of the long term memory immune response have hindered the rational development of vaccines to KFD. These three limitations create challenges in selecting the appropriate antigens to include in a KFD vaccine and achieving durable cross-protective immunity.

Limitations of the Currently Available Formalin Inactivated Vaccines

The existing formalin inactivated CEF vaccine has been developed using classic platforms that were available and appropriate at the time of introduction. The vaccine has been successfully utilized for mitigating disease in endemic KFD areas; however, a number of evaluations of the vaccine in the field have shown that the vaccine elicits waning immunity, has a need for multiple booster doses and variable effectiveness against the vaccine virus in a real world setting [11], [12].

Studies have shown that inactivated vaccines induce less robust T-cell responses compared with live-attenuated or recombinant viral vaccines [13]; therefore, it is expected and has been documented that protective antibody titer declines due to time, particularly for populations that experience repeated exposures (e.g. seasons of exposure) or have not received adequate amounts of the vaccine (e.g. those who have never or infrequently received the vaccine). These factors do not suggest that the existing CEF vaccine has insufficient efficacy against KFD; however, the efficacy of the CEF vaccine may be further enhanced through improvements to the existing CEF vaccine or new vaccines for KFD.

Viral Genetic Variability and Geographical Spread

Although KFDV has been regarded as largely stable from a genetic perspective, numerous studies show that the virus exhibits regional variation as it continues to expand into new ecological niches along the Western Ghats [14], [15]. Even minor differences in the amino acids of viral proteins that dominate immune responses can influence how vaccinated individuals recognize epitopes on that protein, thus limiting the degree of cross-protection afforded by vaccines [14], [16]. The on-going evolution of KFDV is a reason to develop immunization strategies that will focus on dominant epitopes that are conserved among circulating KFDV strains and therefore will be able to provide broad, durable protection.

Community-Level Determinants and KAP Evidence

The increasing geographical reach of KFDV has serious implications for controlling the disease. It requires a robust surveillance system, as well as coordination of responses across state borders, and highlights the need for disease

prevention strategies (improved vaccines that provide broad protection) that can be implemented on a regional basis. The continued expansion of KFDV throughout multiple states will reinforce the argument for implementing comprehensive, preventive, and vaccine-based approaches to control the disease rather than relying solely on localized interventions [17].

In addition to biological limitations, there are also important community-level factors affecting the ability to control KFD in the community setting. In endemic regions, KAP studies show significant variability in KFD awareness, acceptance of vaccination, and adherence to booster shots [11], [18].

Myths and misunderstandings about the virus and KFD have also affected the uptake of vaccines. The belief that vaccines are not safe, concern about side effects, and job-related barriers for forest workers as well as challenges associated with accessing vaccination services, play a significant role in the uptake of vaccines. In addition, most field trials of vaccine efficacy are composite measures of biological efficacy and human behavior, not immunogenicity alone [19]. In the absence of curative therapies, the majority of individuals consider vaccination to be the best preventive measure, and therefore, it is essential for vaccine design and delivery strategies to meet the needs of the community.

Current Vaccine-Centric Control Strategy Based on Absence of Current Therapeutic Options

Currently, there are no approved anti-viral therapies to treat KFD, and the only way to manage patients is through supportive care and symptomatic relief [20]. This includes providing adequate hydration, managing bleeding and keeping a watchful eye for the onset of neurological symptoms [1], [6], [21]. While supportive care can reduce mortality rates if administered in a timely fashion, it does not reduce the amount of virus produced in the body and do not change the progression of the disease [22].

The feasibility of implementing Therapeutic-Based Control Strategies for KFD has many limitations. KFD generally has an acute onset of symptoms and typically has rapid widespread dissemination throughout the body. The onset and dissemination of this disease frequently occurs in remote forest edge areas, where diagnosis is delayed, and access to medical services can be impossible. With these constraints, the therapeutic window for intervention with an anti-viral therapy is drastically shortened [23]. Although broad-spectrum antivirals and flavivirus specific medicines have been studied for use with KFD patient the clinical effectiveness has yet to be proven and no clinical protocols have been established through the use of these types of medications as treatment options [10].

The absence of effective treatments for KFD ultimately supports the case for pursuing next-generation vaccine research as a priority versus de-emphasizing next-generation vaccine research for KFD. By providing protection from the onset of illness, preventive vaccines can address delays in diagnosis and healthcare that negatively impact treatment

success. Advances in reverse-vaccinology, immunoinformatic and epitope-based vaccine design enable identification of conserved antigenic sites, prediction of extensive HLA coverage, and optimization of immune response while minimizing the risk of ADE [24], [25].

Integrated Control Framework for KFD

Control of Kyasanur Forest Disease (KFD) can be accomplished through an integrated system of control, with an emphasis on prevention, and using the following techniques:

- Efficiently designing vaccines using precision vaccinology.
- Communities to develop interventions based on knowledge, attitude, and practice (KAP) studies.
- Improved surveillance systems and ecological awareness.
- Clinician support of patients should occur, even in the absence of treatment.

This approach reflects the understanding that no single intervention will suffice; therefore, sustainable control can only be achieved by combining biological innovation with socio-ecological realities.

Conclusion

The fact that neither an effective vaccine nor a specific therapy exists for KFD highlights the extent of multiple dimensions of complexity associated with the disease (e.g., ecological uncertainty related to KFD occurrence, flavivirus immunology, virus diversity, and community-level factors). This review does not suggest that research is lacking; rather, it underscores the need for integrated research efforts using next generation approaches.

As KFD expands its geographic range, the need for effective KFD control is profound. Expansion poses challenges to both existing surveillance systems and interstate coordination; additionally, the urgency for developing preventive/educational strategies, including effective vaccines that will protect against many circulating KFD viruses, is emphasized. The geographic expansion of KFD across many Indian states reinforces our need for comprehensive, preventive, and vaccine-focused strategies that extend beyond localized efforts.

Currently, the scientific rationale for developing safer, more effective and appropriate KFD vaccines is strong due to the ongoing integration of KAP studies, reverse vaccinology, and next-generation vaccine platforms. The public health burden associated with Kyasanur Forest Disease will be reduced in rural localized regions in endemic areas through the successful development of KFD vaccines.

Abbreviations

KFD-Kyasanur Forest Disease

KFDV – Kyasanur Forest Disease Virus

CEF – Chick Embryo Fibroblast

ADE- Antibody Dependent Enhancement

KAP- Knowledge, Attitude and Practice study

Disclosure of interest

The authors declare that they have no competing interest.

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