International Journal of Advanced Research in Medicine

E-ISSN: 2706-9575
P-ISSN: 2706-9567
IJARM 2023; 5(3): 45-47
Received: 21-05-2023
Accepted: 30-07-2023

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Kyasanur Forest Disease in India: Robust prevention and control strategy is the need of the hour

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DOI: https://doi.org/10.22271/27069567.2023.v5.i3a.500

Abstract
Kyasanur Forest Disease (KFD) is a tick-borne viral haemorrhagic fever endemic to South Asia, caused by the Kyasanur Forest Disease virus (KFDV), a member of the Flaviviridae family. This article highlights the urgent need for a robust prevention and control strategy for KFD in India. The disease primarily affects individuals with occupational exposure to outdoor settings, and transmission occurs through infected ticks primarily from monkeys to humans. Despite being recognized for over six decades, gaps in knowledge persist regarding pathogenesis, host response, and prevention measures. The disease's expansion is facilitated by human intrusion into forests, uncontrolled deforestation, and changing ecological dynamics. The indigenous formalin-inactivated tissue-culture vaccine, the primary preventive measure, exhibits suboptimal efficacy and low coverage. Learning from the Japanese encephalitis experience, the article underscores the importance of a comprehensive strategy based on surveillance, vector control, and targeted vaccination. The development of highly effective vaccines, improved diagnostic methods, and collaborative efforts among health authorities are essential to curbing KFD outbreaks in the future.

Keywords: Kyasanur Forest Disease, Zoonotic disease, Prevention strategy, Vaccination

1. Introduction
Kyasanur Forest disease (KFD) is a tick-borne viral haemorrhagic fever endemic to South Asia. The KFD virus (KFDV) belongs to the family Flaviviridae and genus Flavivirus [1]. People with occupational exposure to rural or outdoor settings (e.g., hunters, herders, forest workers, farmers) in these districts are potentially at risk for infection if they come into contact with infected ticks. The carrier of the virus through ticks is known to dissect on two types of monkeys, known by the nomenclature of black-faced Presbytis entellus and red-faced Macaca radiata [2]. Cases occur in the areas surrounding the forest where there is a wide spread presence of the Haemaphysalis spinigera vector tick [3].
The disease was first reported from Kyasanur Forest of Shimoga district in Karnataka, India in March 1957.The disease first manifested as an epizootic outbreak among monkeys killing several of them. Hence the disease is also locally known as Monkey Disease or Monkey Fever [4].
The disease is endemic in five districts of Karnataka state, India (Shimoga, Uttar Kannada, Dakshina Kannada, Chikmaglur and Udupi). Recently, the cases have also been reported from disticts of Tamil Nadu, Kerala and Goa. The affected districts are all part of the Western Ghats forest (Refer to Table 1). There is also evidence of spread of KFDV in parts of Gujarat and West Bengal [5]. Serological evidence of KFDV has also been found in the Andaman Islands [6].
More recent studies have identified KFDV in Saudi Arabia and the People's Republic of China. The presence of KFDV that has been reported in China and Saudi Arabia showed close genetic similarity with the Indian KFD strains [7, 8].

Transmission cycle
Alteration of ecosystem due to human intrusion may lead to introduction of KFDV from its reservoir host to humans. In KFD, small mammals mostly rodents are considered as the reservoir and act as maintenance host. Other small mammals like shrews and ground birds can also act as reservoir [9]. Infection of wild monkeys occurs through the bite of infected ticks and further spread to other non-infected ticks and monkeys.

Human's contract infection mainly through the bite of infected nymph and also by contact with infected animals especially monkeys [9]. Man is a dead –end or tangential host and of no significance in the natural history of the KFDV. There is no evidence of person to person transmission of KFDV [10]. The disease has been known for more than six decades, but no hospital has ever reported any nosocomial KFD infections or cases, which occurred between close human contacts.

Clinical features, diagnosis and treatment

The onset is sudden with chills, frontal headache and high fever. The clinical symptoms include continuous fever for 12 days or longer, usually associated with severe myalgia, cough, diarrhea, vomiting and photophobia. The incubation period is of 2-7 days. The convalescent phase is prolonged. Often, there is a relapse after 1 to 2 weeks of a febrile period. The second phase lasts for 2- 12 days and is marked by the same symptoms. Neck stiffness, mental disturbance, giddiness and abnormality of reflexes are additional complications in the second phase of illness. Human disease is characterized by an incubation period of ≈3–8 days, followed by chills, frontal headache, body ache, and high fever for 5–12 days, and a case-fatality rate >30% [11]. Viremia lasts for around 12-13 days and remains high during the first 3 to 6 days [12].

The clinical signs of KFD are similar to other viral/ haemorrhagic fevers. The diagnosis is made by virus isolation from blood or by serologic testing using enzyme-linked immunosorbent serologic assay (ELISA). Recent developments include a nested RT-PCR and a Taq Man-based real time RT-PCR [13].

There is no specific treatment except supportive and symptomatic ones. Analgesics, maintenance of hydration and nutrition along with rest are the mainstay of treatment. Blood transfusion is done if the situation demands. No particular measures of isolation of patients seem to be indicated.

Preventive measures

The chance of transmission of KFD to humans is increasing due to rapid, uncontrolled deforestation and along with increased human activities in forest area without protective measure. Prevention strategies such as quarantine, vaccination, early diagnosis, tick control will restrict the entry of virus to new areas. The KFDV has been classified as risk group IV pathogen. Vaccination is one of the main control strategies for KFD. Other control strategy includes wearing protective clothing while handling infectious materials and tick control. Strictly prohibit the visit to affected forest areas during outbreak time. If visit is inevitable, use protective clothing's and gum boots to cover the whole body and apply some insect repellent to exposed body part.

Vaccination

Vaccination with indigenous formalin-inactivated tissue-culture vaccine has been the primary strategy for controlling KFD. Vaccination is being done in India since 1990. The vaccine being used is a liquid freeze sensitive vaccine to be stored in +2 to +8 degree Celsius.

The strategy involves mass vaccination in areas reporting KFD activity (i.e., laboratory evidence of KFD virus in monkeys, humans, or ticks) and in villages within a 5-km radius of such areas. Two vaccine doses are administered at least 1 month apart to persons 7–65 years of age. Vaccine-induced immunity is short-lived, so the first booster dose of vaccine is recommended within 6–9 months after primary vaccination; thereafter, annual booster doses are recommended for 5 years after the last confirmed case in the area [14]. The vaccine is given subcutaneously 0.5 ml dose to children (6 to 14 years) and 1 ml to adults (15-65 years).

Earlier studies have reported high effectiveness of the vaccine during 1990–92 in affected districts of Karnataka, an effectiveness of 79.3% (95% CI: 64.7–87.9) with one dose and 93.5% (95% CI: 87.9–96.6) with two doses but still KFD cases among vaccinated individuals were reported indicating sub-optimal efficacy of the vaccine used or vaccination protocol [15].

As per a case surveillance study conducted recently in Karnataka, the effectiveness of the KFD vaccine is lower as compared to the earlier reports, especially after a single dose administration. The effectiveness of the vaccine analysed was 62.4% (95% CI = 26.1–80.8) among those who received two doses and 82.9% (95% CI = 71.3–89.8) for those who received an additional booster dose as compared to the unvaccinated individuals. In particular, the administration of one dose was found to be non-efficacious as the incidence of the disease among such individuals was comparable with unvaccinated individuals [16].

Currently, there are aggressive vaccination efforts are going on in the affected states but ongoing surveillance activities have indicated low vaccine coverage, and spread of disease to areas beyond those selected for vaccination and to age groups not targeted for vaccination. This is a matter of concern as despite of extensive vaccination campaigns an increasing number of KFD cases have been detected in the endemic states.

Discussion

Kyasanur forest disease (KFD) remains largely a neglected and unaddressed disease despite reports of recent outbreaks. There are significant gaps in the knowledge of the disease, including many aspects of its pathogenesis, the host response to infection and potential prevention and therapeutic options.

The current known distribution of KFDV is limited to relatively restricted areas of India, Saudi Arabia and China but the possibility that KFDV does exist in other areas of the world in cryptic enzootic cycles cannot be ruled out. Due to the expanding population and the ecological and geographic changes such as intrusion into forest by humans and large scale deforestation with associated tick displacement, there is a high possibility of KFDV in other areas. Now, with the availability of modern diagnostic methods like ELISA and PCR, the presence of this virus in many previously unknown KFD areas has come into light. It is required that rapid and easy-to- use diagnostic tests are developed for conducting field level sero-surveys in different regions of the country which would help in the mapping of the disease. There is also a need to establish an event-based surveillance system for monkey deaths in the national parks, wildlife sanctuaries, and reserve forests of the Western Ghats, as well as neighbouring areas. This would help detect the disease early and thereby help institute appropriate control measures [17].

An indigenous formalin-inactivated tissue-culture vaccine is being currently used for prevention of KFD but studies have

indicated the low effectiveness of the vaccine. Also, in spite of extensive vaccination campaigns in the endemic areas, the vaccination coverage is found to be very low. It is important that an evaluation is planned to understand reasons for the vaccine's low coverage, evaluate the appropriateness of the vaccination strategy and evaluate the issues related with cold chain maintenance. The vaccine associated side effects such as pain as well as the number of doses to be taken over a period of five years are also some potential deterring factors for uptake of the vaccine. There is a need to focus on conducting research to develop newer highly effective and safe vaccines and avoiding the need for periodic boosters.

Learning from the Japanese encephalitis (JE) vaccination experience, immunization strategy for KFD in India should be developed based on the 3 pillars of prevention and control i.e., Surveillance for cases of KFD, Vector control and Vaccination [18]. Like JE, KFD is also not a uniformly distributed disease, therefore targeted immunization approach will be the most cost effective. It is required that a strong KFD vaccination policy is developed jointly by National Vector Borne Disease Control Programme (NVBDCP), and Immunization division of Ministry of Health and Family welfare with support from Immunization development partners to prevent outbreaks in the future.

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How to Cite This Article
Juneja S. Kyasanur Forest Disease in India: robust prevention and control strategy is the need of the hour. International Journal of Advanced Research in Medicine 2023; 5(3): 45-47.