CD ALERT

NATIONAL CENTRE FOR DISEASE CONTROL
DIRECTORATE GENERAL OF HEALTH SERVICES

KYASANUR FOREST DISEASE: A PUBLIC HEALTH CONCERN

1. INTRODUCTION

Kyasanur Forest Disease (KFD) is a re-emerging zoonotic disease associated with sudden onset of high grade fever, prostration, nausea, vomiting, diarrhea and occasionally neurological & haemorrhagic manifestations. The KFD virus is a member of the genus *flavivirus* and family *Flaviviridae*. It is transmitted to man by bite of infected ticks. This disease was first discovered in 1957 from Kyasanur forest area, Shimoga district of Karnataka state in southern India. It derives its name from the forest range where the virus was first isolated. It is also known as "monkey disease/monkey fever" because of its association with monkey deaths.

1.1 Global situation

The KFD virus was initially suspected as a Russian spring–summer (RSS) complex of viruses. As of now, KFD is only reported from India. The other viruses which are closely related to KFD are Omsk hemorrhagic fever virus in Siberia, Alkhurma virus in Saudi Arabia and Nanjianyin virus in China.

1.2 Indian scenario

The disease was first reported in 1957 from Shimoga district, Karnataka, which is a primitive sylvan territory in Western Ghats of India, subsequently spread centripetally to other districts of Karnataka viz., Chikkamagalore, Uttara Kannada, Dakshina Kannada and Udupi districts and to Chamarajanagar district in 2012 and most recently to Belagavi district in 2016. In 2013, KFDV was detected in autopsy material of dead monkeys in Nilgiris district of Tamil Nadu state. Monkey deaths and human cases have now been reported from three neighbouring states bordering Karnataka viz., Wayanad (2013) and Malappuram districts of Kerala (2014), North Goa district of Goa state (2015) and Sindhudurg district of Maharashtra (2016).

Fig.1 KFD affected states in India

2. EPIDEMIOLOGY

2.1 Agent:

The KFD virus (KFDV) is immunologically close to Alkhurma virus. This RNA virus measuring about 25nm in diameter. The positive-sense RNA genome of the KFDV is about 11 kb in length and encodes a single polyprotein that is cleaved post translationally into three structural (C, M and E) and seven non-structural (NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5) proteins.

2.2 Natural host, reservoir & vector

A number of forest dwelling small mammals like rodents, shrews, insectivorous bat and many birds maintain the natural enzootic cycle of the virus in the forest ecosystem. The wild primates, black faced langurs (*Semnopithecus entellus*) and red faced bonnet monkeys (*Macaca radiata*) get the virus infection by tick bite and are susceptible to the infection. Man is an incidental dead end host. Cattle are very important in maintaining tick population.

The hard ticks belonging to family *Ixodidae* of the genera *Haemaphysalis* are the reservoirs as well as vectors of the virus. The important ticks known to transmit KFD include: *Haemaphysalis spinigera, H. turturis, H. kyasaurensis, H. kinneari, H. papuana H. wellingtoni, H. minuta, H. cuspidata, H. bispinsosa, Dermacentor auratus and Ixodes petauristae.*

Ticks are obligate haematophagosecto-parasites of mammals, birds and reptiles. The major vector ticks *Haemophysalis spinigera* and *H. turturis* found to inhabit the forest floors and vegetation and also infest various small mammals and birds. Humans become infected through the bite of infected unfed nymphs, which appear to be more anthropophilic than mature ticks. The KFD virus is transmitted from infected larva to nymph to adult maintain the transovrial and transtadial transmission of virus in the ecosytem.

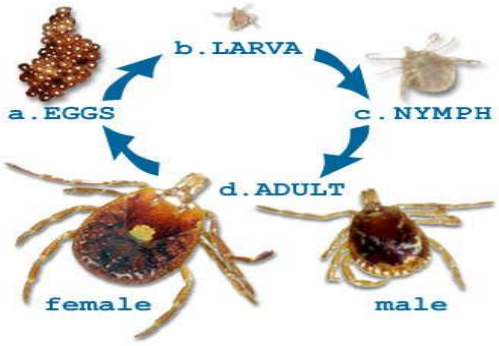

Fig 2: Life Cycle of Hard Tick (Geevarghese G and Mishra AC **2011**)

2.3 Environmental factors

The epidemic period usually begins in October or November and peaks from January to April, then declines by May and June. The epidemic/ outbreaks relates to the activity of nymphs, which is very high during November to May. Adult fed female ticks lay eggs, which hatch to larvae under the leaves. They further infest small mammals and monkeys, as well as accidentally infest humans, and feed on their hosts. Subsequently, they mature to nymphs, and the cycle is repeated. Nymphs and adults also transmit the disease to rodents and rabbits by bite, and this rodent–tick cycle continues for more than one lifecycle.

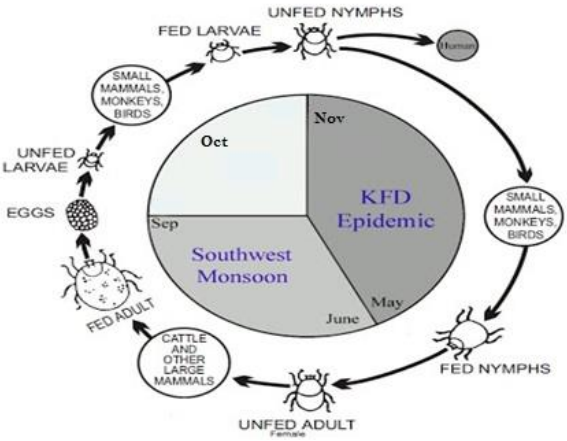

Fig 3: Stages of development of Haemaphysalis spinigera (ticks) responsible for transmission of KFDV to humans

2.4 Mode of transmission:

KFDV is transmitted by an infected tick, especially nymphal stage ticks. The wild monkeys *Semnopithecus entellus and Macaca radiata*, gets the disease through the bites of infected ticks. Infection causes severe febrile illness in most of the monkeys. When infected monkeys die, the ticks drop from their body, thereby generating "hot spots" of infectious ticks that further spread the disease. Humans can get the disease form an infected tick bite or by contact with an infected animal,

such as sick or recently dead monkey. Available epidemiological data does not suggest any human-to-human transmission. However, human cases have been reported in the past while working on this virus in the laboratory.

2.5 Incubation period

Estimated to be between 3-8 days after the bite of an infective tick.

3. CLINICAL FEATURES

Kyasanur forest disease (KFD) usually presents with sudden onset of high-grade fever with chills, intense frontal headache, severe myalgia and body aches. Muscle tenderness, photophobia, nausea, vomiting, and diarrhea are usually seen. Respiratory symptoms like persistent cough, may be present in some cases. Temperature may be as high as 104^0 F/40^0C, and last for 5-12 days and there is intense prostration. In few cases hemorrhagic symptoms may occur in early stage in the form of bleeding from the nose, gums and intestines as evidenced by hematemesis or fresh blood in the stools. Some patients have persistent cough, with blood-tinged sputum and occasionally substantial hemoptysis but generally resolve soon. There may be cervical, axillary and epi-trochlear lymphadenopathy. A papilo-vesicular lesion in the soft palate is observed as a constant finding in most cases.

In severe cases neurological symptoms like neck stiffness, mental disturbance, coarse tremors, giddiness, and abnormality of reflexes are noted. Un-treated cases rapidly progress to convulsions, coma and death. Few cases show a biphasic picture of illness. The second phase of the illness occurs after the febrile phase, on an average, from day 8 onwards. This phase is initiated by headache, severe prostration progressing to signs and symptoms of central nervous system involvement in very few cases presenting as meningo-encephalitis. Hemorrhagic manifestations can occur in both phases, and severe bleeding from various sites can lead to shock and death.

Case fatality is 2-10%. Fatality is higher in the elderly and in patients with co-morbid conditions like - liver diseases (alcoholic) etc.

Differential diagnosis: Dengue/DHF, typhoid, malaria, rickettsial infections, leptospirosis and other viral haemorrhagic fevers.

Case definition

Presumptive case:

A patient of any age presenting with acute onset of high grade fever with any of the following:

Headache/ Myalgia/ Prostration/ Extreme weakness/ Nausea/ Vomiting/ Diarrhea/ Occasionally neurological/ haemorrhagic manifestations.

AND/ OR

- Rule out common etiologies of acute febrile illness prevalent in the area (Dengue/DHF, typhoid, malaria etc.,)
- History of exposure to tick bite
- Travel and/ or Living in and around forest area where laboratory confirmed KFD cases have been reported previously or an area where recent monkey deaths have been reported*

Confirmed case:

A presumptive case, which is laboratory-confirmed by any one of the following assays:

- Detection of KFDV-specific viral RNA by reverse transcription polymerase chain reaction (RT-PCR) or real time RT-PCR from blood or tissues.
- Isolation of KFDV in cell culture or in a mouse model, from blood or tissues.
- Positive for immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) for KFD. (Considered Lab Confirmed for Operational Purposes)

* As per State Government of Karnataka policy, area in a radius of 5 km from where recent monkey deaths have been reported, is considered as potential exposure zone. Local authorities may decide operational zone as per their own requirements.
Note: Suggestive case definitions are provided for the reference. However, local public health experts may be consulted.

4 DIAGNOSIS

Human blood samples, monkey viscera and ticks collected from the field are tested for KFDV. Samples are tested by either real time RT-PCR or IgM ELISA methods. In the acute febrile phase KFD laboratory confirmation is done by real time RT- PCR assay. In the subsequent weeks, it can be confirmed by anti-KFDV IgM ELISA assay.

4.1 Sample collection and transportation

Collection of serum from suspected patients

Collect 4-5 ml blood in a plain vial. Separate the serum following standard biosafety precaution.

Collection of Monkey viscera

Collect Brain, Lungs, Heart, Liver and Kidney specimens from the dead monkey following standard biosafety precaution.

Tick collection

Collect nymph tick and keep in a sterilised Polypropylene container. The tubes should be air tight and sealed in plastic bags so that vial should not open during transportation and infected ticks spread in newer areas.

Sample Storage: Keep serum of human cases/ viscera of monkeys/ tick samples refrigerated (2-8 degree C) if it is to be processed (or sent to a reference laboratory) within 48 hours. Keep frozen (-10 to -20 degree C), if it is to be processed after a week. The sample can be preserved for extended periods.

Transportation of the sample to the reference laboratory: Always use triple layer packaging and ship within 48 hours of collection under cold chain (dry ice or at least with cooling gels). The original samples should be packed, labeled and marked. Always include the completely filled out clinical and epidemiological record.

The designated laboratory for diagnosis and isolation of KFDV in humans, monkey necropsy samples and ticks is:

- National Institute of Virology

Microbial Containment Complex, 130/1 Sus Road. Pashan, India Pune 411021
Tel.No.: 91-020-26006390
Fax No.: 91-020-25871895

Also designated laboratories for diagnosis of KFDV in human samples are as follows:

- Virus Diagnostic Laboratory Opp. Scout Bhawan, B H Road, Shimoga, Karnataka State
  Tel: +91-0812-222050
  Email ddvdlsmg@gmail.com

- Manipal Academy of Higher Education (Deemed to be University)
  Madhav Nagar, Manipal - 576 104
  Karnataka State, India.
  Tel: +91 820 2922663
  Fax: +91 820 2922718
  Email virology@manipal.edu

The samples for diagnosis of the disease in suspected human cases can be sent to above-mentioned designated laboratories.

4.2 Laboratory techniques

Detection of KFDV by real-time RT-PCR and RT-PCR. These are the first line of tests for the diagnosis of KFD. Real-time RT-PCR can detect the virus in samples after onset of febrile illness up to the 8th day.

KFD IgM antibodies by enzyme-linked immunosorbent assay (ELISA): KFD IgM antibody can be detected from 5th day of onset of symptoms till 3 months.

Isolation of virus: In patients with KFD infection the level of viremia reaches up to 3×10^6 within 3–6 days and remains high detectable level by PCRs up to 8 days of infection. Virus can be isolated by inoculation into infant mice or in cell culture (Vero E6, BHK-21 or Chick embryo cells. Virus isolation from KFDV positive samples should be carried out in BSL-3 laboratory.

5. TREATMENT

No specific treatment for KFD is available; however, prompt symptomatic and supportive therapy including maintenance of hydration, hemodynamic stability and management of neurological symptoms decreases morbidity and mortality.

6. PREVENTION AND CONTROL

6.1 Surveillance:

KFD surveillance consists of three major components:

- Human surveillance: Early detection of patients, prompt laboratory diagnosis and proper management of patients is very important. Passive routine surveillance and routine review of the surveillance data to be done under IDSP to detect impending outbreaks of KFD. Event-based surveillance of unusual suspected KFD cases/deaths to be done in the control and containment.
- Monkey surveillance: The surveillance on death of monkey/ monkeys in non-endemic as well as endemic areas of KFD to be carried out regularly in real time manner in collaboration with Forest and Veterinary Department. Human cases can be suspected in case of unusual monkey death.
- Tick surveillance: Tick surveillance and tick mapping for identifying hotspots and tick incrimination studies in KFD prone areas for monitoring tick positivity for KFD to be carried out regularly on periodic basis.

6.2 Personal protection:

Application of repellants such as Dimethylphthalate (DMP), NN-Diethyl-m-Tolumaide (DEET) and certain other proprietary preparations having these or similar chemicals, e.g. Mylol on the exposed parts is effective from one to a few hours. If the duration of stay inside the forest is longer, more than one application may be necessary. People living in the forest or visiting forest areas should strictly use tick repellents along with personal protection measures (long clothes by covering neck, chest, back, and legs) before going to the forest.

6.3 Vaccination

There is limited availability of information on KFD vaccine for human use in India.

Note: State Government of Karnataka is following KFD vaccination policy in the KFD endemic area, other States reporting KFD may decide respective vaccination policy for KFD accordingly. KFD vaccine is formalin inactivated tissue culture vaccine. It is currently manufactured at Institute of Animal Health & Veterinary Biologicals, Hebbal, Bengaluru for Department of Health & Family Welfare, Government of Karnataka. However, Karnataka government has successfully used KFD vaccines in few affected districts in outbreak situation.

6.4 IEC: Routine IEC activities to be conducted by field staff to educate people about disease and make them accept vaccine. There seems to be a need to approach people with focused, sustained innovative local mass media campaigns supplementing traditional interpersonal

Communication for the success of KFD control programme. The IEC can be done by as follows;

- Approaching vaccination campaign in mission mode just like Pulse polio
- Conducting regular annual sensitization program for Veterinary department, Forest department officials, ASHA, Education department and Gram Panchayath officials
- ASHA incentives for assistance during vaccination especially for mobilizing and encouraging public to take vaccine
- Pre-vaccination IEC campaigns
- Intense and focused IEC campaign involving all possible media

6.5 Tick control

Source reduction: The spraying of insecticide like Malathion may be carried out in areas where monkey deaths have been reported within a radius of 50 meters around the spot of the monkey death (Manual on Kyasanur Forest Disease, 2005). It is also effective in forest tracks frequently visited by people for various activities.

Vector control: Vector control may be done by dusting with Malathion or by spraying with pyrethroids. Repellents may be used on body/exposed parts during venture into forests. Application of insecticide on cattle can prevent transportation of ticks from forests to dwelling premises.

Physical control: Controlled burning of the dry leaves and bushes in the forest boundaries, premises of human habitats.

6.6 Inter-sectoral coordination

KFD has multidimensional risk factors for its transmission and sustenance. Looking at various aspects of KFD epidemiology, inter sectoral coordination is vital to implement various preventive & control measures effectively. Health department, Veterinary Public Health department, Forest and Wild life departments, Vector control division, District administration, Tribal welfare, Fire control departments, and many more are the key stake holders in its control. Each of the stakeholders has to be clear about their roles and responsibilities. Meticulous division of labour amongst all these departments is essential to have more coordinated efforts. State & district authority should chalk out responsibilities of various departments.

Fig 4: Kyasanuru Village in Sorab Taluk, Shimoga District of Karnataka.

Table 1. Responsibilities of various departments in the district:

Sr. No	Department	Responsibilities
1	Public Health	• Surveillance • Field investigation, hot spots identification. • Vector study and vector control measures. • Laboratory Services • Clinical Management of cases/ Referral arrangements. • Protocols for primary/secondary and tertiary care • KFD Vaccination • Tick control activities • Health Education to masses • Vaccination of the vulnerable groups. • Reporting to SSU/State Health directorate. • Media management. • Engagement with all stakeholders.
2	Animal Husbandry and Veterinary Colleges/ Institutes	• Tick control in domestic animals in villages near the periphery of KFD endemic areas • Postmortem of dead monkeys wherever necessary • Collection of tissue samples from dead monkeys for KFD detection. • IEC and Advocacy efforts in the district. • Support in vector identification and surveillance. • Participation in multidisciplinary RRT investigations. • Technical support for tick control among domestic animals.
3	Forestry	• Detecting and reporting of monkey deaths to the concerned • Disposal of dead monkeys in collaboration with other stakeholders • Declaration of Hot spot & tick control at hot spot areas • Ensured personal protection of all laborers in forest. • Facilitate vector control in tick infested spots/monkey death spots. • Strict vigil on all entering/leaving reserve forest areas. • Widespread IEC displayed in hotspots. • Guided all investigating teams into the deep forest areas.
4	Wild life	• Arrangement for autopsy of dead monkeys. • Arrangements for capturing sick monkeys. • Isolation and care of sick monkeys. • Coordination with district authorities in unexpected Law & Order situations. • Support to other departments.
5	Tribal welfare	• Tribal health promoters to support surveillance activities. • Ambulance support for referral of cases to Hospitals. • Arrangement for organizing Medical Camps in all difficult to reach colonies.
6	Revenue department	• Financial support for the KFD activities
7	Education department	• Vaccination and IEC activities coordination in Schools • Information to the surveillance system
8	Women and child welfare	• Taking services of Anganawadi workers, where there is no availability of ASHA
9	Information and broadcasting department	• Dissemination on IEC
10	NGOs	• Support surveillance and IEC activities.

Important points to remember:

Do's

- Report monkey deaths to Animal husbandry/forest officials and /or Health Department OR Health Authority.
- Persons, who are visiting/working in the forest, should cover body with full clothes.
- Apply tick repellents like DMP oil to the exposed parts before going to forest.
- Wash the clothes and body with hot water and soap after returning from the forest.
- Report of incidence of the disease/deaths, which occurs as high fever with severe head ache and body ache to nearest health facility.
- Educate the villagers to avoid the forests areas where monkeys have died.
- Bring to the notice of the Health Department or Department Hospitals or Private Hospitals, regarding any serious cases in the villages or from KFD affected areas, which require immediate symptomatic treatment.
- Ectoparasite (tick) control in cattle and domestic animals will help in reducing the density of tick's population.

Don'ts

- Don't bring the leaves of trees from KFD infected area to the village for cattle bedding material.
- Don't visit the area where recent monkey death is been reported, especially an area where case of KFD has been reported in the past.
- Don't handle the infected monkey carcass by bare hand without personal protective equipment.

For Further Reading:

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The expert group meetings for preparation of Guidelines for Prevention & Control of Kyasanur Forest Disease was held on 12.04.2017 and 20.02.2018 at NCDC Delhi. The following participants were worked on preparation of Guidelines for Prevention & Control of Kyasanur Forest Disease.

S. No.	Name	Designation & Place of posting
1	Dr S Venkatesh	Ex-Director, NCDC, Delhi
2	Dr H K Muniyellappa	Ex-Joint Commissioner (Livestock Health), Department of Animal Husbandry Dairying and Fisheries, Delhi
3	Dr Manoj Murhekar	Director, National Institute of Epidemiology (NIE), Chennai
4	Dr S M Byregowda	Director, Institute of Animal Health & Veterinary Biologicals (IAH & VB), Bengaluru
5	Dr Rubina Bose	Deputy Drugs Controller (INDIA), Central Drugs Standard Control Organization (CDSCO), New Delhi
6	Dr N Balakrishanan	Ex Joint Director, NCDC Bengaluru branch, Bengaluru
7	Dr G Arunkumar	Prof. & Head, Manipal Center for Virus Research (MCVR), Manipal
8	Dr B S Jayaram	Deputy Director, Animal Disease Surveillance Scheme (ADSS), Hebbal, Bengaluru
9	Dr Pradip Awate	State Surveillance Officer, IDSP, Maharasthra
10	Dr Utkarsh Betodkar	State Surveillance Officer, IDSP, Goa
11	Dr Ashok M	Scientist, National Institute of Virology (NIV), Bengaluru Unit, Bengaluru
12	Dr A. Sukumaran	State Epidemiologist, IDSP, Kerala
13	Dr Kiran S K	Taluk Health Officer, Thirthahalli, Shivamogga, Karnataka
14	Dr Arun Kumar Bansal	HOD & Additional Director, Malariology & Coordination Division, NCDC, Delhi
15	Dr Mala Chhabra	Ex HOD & Additional Director, Zoonosis Division, NCDC, Delhi
16	Dr A Shrivastava	HOD, Centre for Environmental and Occupational Health Division, NCDC, Delhi
17	Dr Pradeep Khasnobis	Joint Director, CSU (IDSP), NCDC, Delhi
18	Dr Naveen Gupta	HoD, Zoonosis Division, NCDC, Delhi
19	Dr Arti Bahl	Joint Director, Epidemiology Division, NCDC, Delhi
20	Dr Sanket V Kulkarni	Deputy Director, CSU (IDSP), NCDC, Delhi
21	Dr Ruchi Jain	Deputy Director, CSU (IDSP), NCDC, Delhi
22	Dr Simmi Tiwari	Deputy Director, Zoonosis Division, NCDC, Delhi
23	Dr Monil Singhai	Assistant Director, Zoonosis Division, NCDC, Delhi
24	Dr Mahesh Waghmare	Assistant Director, Microbiology Division, NCDC, Delhi
25	Dr Ajit Shewale	Assistant Director, Zoonosis Division, NCDC, Delhi
26	Dr Ashok Kumar Talyan	EIS Officer, NCDC, Delhi
27	Dr Rajkumari Mandakini Devi	Deputy Assistant Director, Zoonosis Division, Delhi
28	Dr C S Sahukar	Veterinary Consultant, Zoonosis Division, Delhi
29	Dr Nataraju S M	Veterinary Consultant, CSU (IDSP), NCDC, Delhi
***Experts from various specialities have contributed in relevant areas.**		

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Director, National Centre for Disease Control, 22 Shamnath Marg, Delhi 110 054
Tel: 011-23971272, 23971060 Fax: 011-23922677; E-mail: dirnicd@nic.in;
Website: www.ncdc.gov.in