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A TICK BORN VIRAL DISEASES: KYASANUR FOREST DISEASE AND CRIMEAN-CONGO HAEMORRHAGIC FEVER IN INDIA

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ABSTRACT

Ticks are distributed worldwide and transmit the pathogenic microorganisms that affect humans. Most of the tick borne diseases are caused by tick borne viruses. Two main tick borne diseases Kyasanur forest disease (KFD) and Crimean-congo haemorrhagic fever (CCHF) are found in India with high mortality rate. KFD is a tick born disease caused by a vector Haemaphysalis spinigera. It was first observed in 1957 Karnataka state, India which also affects nonhuman primates. The newer cases were reported from the areas of Kerala, Tamil Nadu and Goa state. No specific treatment of KFD is available; but the supportive therapy is important to minimize the symptoms and formalin inactivated KFDV vaccine is currently in use to prevent KFD infection. CCHF is distributed in Asia, Africa and some part of Europe, but the existence of CCHF in India was first confirmed in 2011 in Gujarat state. Hyolomma spp. ticks are the vector for the transmission of CCHF. There is a need for improved diagnostic facilities, more containment laboratories, better public awareness, and implementation of thorough tick control in affected areas during epidemics.

Keywords: Crimean-Congo hemorrhagic fever, India, Kyasanur forest disease, Tick borne diseases.

I. INTRODUCTION

Globally, the arthropod vectors like ticks are important for transmission of numerous infectious agents and are responsible for causing human and animal diseases [1]. Ticks are essential bloodsucking ectoparasites that infest mammals, birds, reptiles and amphibians [2]. Considering the total world's tick fauna 80% of are hard ticks and the remaining 20% are soft ticks. In the transmission of disease to domestic animals and humans only 10% of the total hard and soft tick species are known to be involved [3]. Tick-borne diseases are prevalent only in specific risk areas where favorable environmental conditions exist for individual tick species [4]. The tick-borne

viral diseases generally manifest three different clinical conditions such as encephalitis, haemorrhagic fevers, and acute febrile illness [5].

Haemaphysalis spinigera and Hyalomma anatolicum are the two important species of ticks present in India, which is responsible for causing the fatal tick-borne viral diseases Kyasanur forest disease and Crimean-Congo hemorrhagic fever respectively [6, 7]. The highly infectious nature of KFD and CCHF causes the outbreak of these diseases to newer areas. This paper focuses particularly on the Indian scenario of KFD infection, clinical and epidemiological features of the disease, and current policies for management of their control and for raising public awareness.

II. TICK BORNE VIRAL DISEASES IN INDIA

2.1 Kyasanur forest disease

KFD is a historically understudied tick-borne disease that affects hundreds of people each year in India. KFDV was first isolated during an outbreak of febrile disease in 1957 in people living in the Kyasanur forest area of the Shimoga district in the Karnataka (then Mysore) state of India [8, 9]. The KFD virus is a member of the genus Flavivirus and family Flaviviridae. The virus was initially suspected as a Russian spring–summer (RSS) complex of viruses, since isolates from monkeys and human showed relatedness to this virus [10].

2.1.1 Mode of transmission

KFDV is transmitted to the wild monkeys *Presbytis entellus* (black faced langur) and the red faced bonnet (*Macaca radiate*), through the bites of infected *H. spinigera* ticks [8]. After infection, KFDV is transmitted to other ticks feeding on the infected animals. Infection causes severe febrile illness in some monkeys. When infected monkeys die, the ticks drop from their body, thereby generating hotspots of infectious ticks that further spread the virus. The genus Haemaphysalis includes 177 species. All Haemaphysalis spp. are three-host ticks. H. spinigera is the main vector of KFD, which is endemic in Karnataka state, India [11]. Humans become infected through the bite of infected unfed nymphs, which appear to be more anthropophilic than mature ticks [12]. Ticks have also been found to transmit this virus, thus also acting as a reservoir for the virus. The Fig. 1 represents the life cycle of vector and mode of transmission of KFD.

2.1.2 Geological distribution of KFDV in India

In the forest area of Shimoga district Karnataka, India during 1956 large number of monkey mortality were reported followed by acute, febrile haemorrhagic disease in humans nearby [13]. The name Kyasanur Forest disease was given after the forest where the first viral isolate was obtained [14]. After the discovery of KFD it is confined to three talukas Sagar, Shikaripur and Sorab of the Shimoga district of Karnataka, until 1972. Thereafter, it was reported from four additional areas, namely Chikmagalur, Dakshina Kannada, Udipi and Uttar Kanada districts of Karnataka state [15]. Around 400–500 cases of KFD are reporting from India every year [9]. In every season of epidemic, around 500 cases are reporting from these areas [15, 16].

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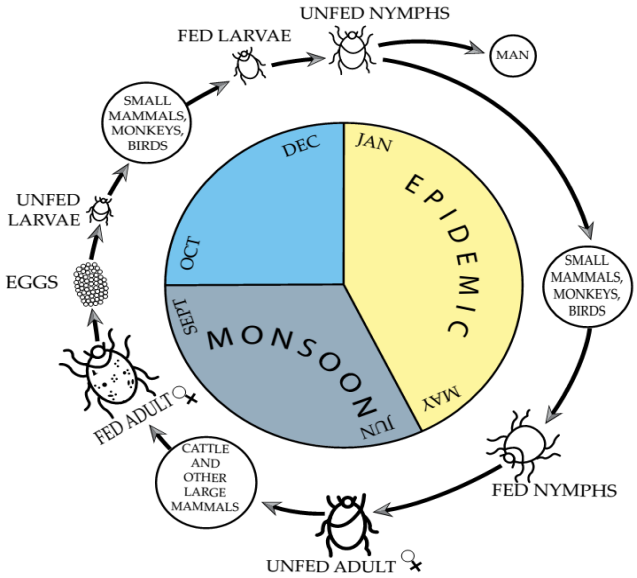

Figure 1: Mode of transmission of KFD virus

Between 2003 and March 2012, there were 3263 reported human cases and, of these, 823 were laboratory confirmed. Large numbers of human infections were reported in 2003–2004, but a significant decline occurred in 2007 and again in 2010–2011 [17, 18]. In 2013, KFDV was detected in autopsy of dead monkeys in Nilgiris District, Tamil Nadu and in a one incidence of human case from Wayanad district, Kerala [19]. Serological evidences are there for the probable existence of KFDV in different states of India [20]. The KFD is placed in the biosafety risk group-4 category as per the guidelines of the Center for Disease Control and Prevention [21].

2.1.3 Clinical signs and symptoms

In humans, the incubation period of KFD is estimated to be about 2 to 7 days after tick bites or exposure [8]. The onset is sudden and followed by headache and fever which rapidly rises to 104^0F. The initial prodomal stage lasts for around one week, with sudden onset of fever, chills, headache, gastro intestinal disturbances, insomnia, sore throat, decreased blood pressure and heart rate, pain in muscles, extremities and conjunctivitis. Humans infected with KFDV have low platelet, white blood cells and red blood cells count. Ophthalmic manifestations of KFD are haemorrhages in conjunctiva, retina and vitreous humour, keratitis, opacity of lens, mild iritis [22, 23].

The next haemorrhagic stage is characterised by irregular epistaxis with blood in vomitus and faeces, blisters on mouth, haemorrhages from the gum and nose. The haemorragic stage is followed by a long convalescent stage. The fever last for 2-12 days. Frequently, a second febrile stage of around 2 weeks with same clinical manifestations of first phase along with various neurological complications was reported. Abnormal reflexes, confusion and tremors noticed as neurological complication [24-26].

2.1.4 Diagnosis

The clinical signs of KFD are similar to many other viral/ haemorrhagic fevers. There should be a reliable and fast differential diagnostic test for confirmation of KFD. Earlier for KFD detection, virus isolation and some antibody based detection methods such as hemagglutination inhibition (HI), complement fixation (CF) and

neutralization test (NT) were used [27]. With advancement of technologies, laboratories developed various molecular diagnostic methods for diagnosis. After establishment of the first BSL-3 laboratory of India at NIV, Pune, real-time RT-PCR, RT-PCR and detection of IgM and IgG antibodies by ELISA were developed and standardized [8].

Virus isolation of KFDV can be done by in vitro using BHK–21, Vero E6 cell lines and embryonated chick cell or in mice [28, 29]. KFD anti-IgM antibodies can be detected using ELISA during the acute phase [21]. RT–PCR and real time PCR provides a very rapid and accurate diagnosis [30]. The RT–PCR reactions are highly specific and sensitive compared to other conventional methods [31-33].

2.1.5 Treatment

Currently, no specific antiviral treatment exists for KFDV in humans; early hospitalization and supportive treatment becomes more essential. Supportive therapy includes the maintenance of normal blood cell counts, blood pressure and hydration [34]. Also the pain relief drugs like antipyretics, blood transfusion, and antimicrobial therapy for secondary infections, corticosteroids and anticonvulsants for nervous disorders [24].

2.1.6 Prevention and control

Tick borne diseases are emerging as a result of changes in public health policy, acaricide resistance, climatic changes, and emergence of new variant of pathogen. Measures need to be taken for reversal of these conditions [35]. Prevention strategies such as quarantine, vaccination, early diagnosis, tick control will restrict the entry of virus to new areas. Vaccination is one of the main control strategies for KFD. Formalin inactivated tissue culture vaccines are available for immunization against KFDV in endemic areas. Other control strategy includes wearing protective clothing while handling infectious materials and tick control.

Use of tick repellent should be advised to the local villagers, forest camp workers and staff, tourist and wild-life photographers. Benzenehexachloride (BHC) spraying may be carried out in areas where monkey deaths have been reported. Strictly prohibit the visit to affected forest areas during outbreak time [5, 36-37]. An inactivated or killed tissue culture vaccine has been used in endemic areas of Karnataka, India since 1990. Initially 2 doses were used in persons of 7– 65 years of age, in an interval of 4 weeks. Revaccination is required after 6–9 months for five years [17]. The efficiency of vaccine was around 62% in individuals received initial 2 doses and 83% in individuals who received further boosters.

2.2 Crimean-Congo haemorrhagic fever

CCHF was predictable for the first time in 1944, in the West Crimean region of the former Soviet Union, during a large outbreak, and the virus was afterward isolated in 1956 from a human case [38, 39]. The Crimean–Congo haemorrhagic fever virus (CCHFV) is also considered as an important zoonotic virus, owing to its wide distribution and ability to cause disease in humans, with high mortality rate [40]. It is a member of the genus *Nairovirus* of the family Bunyaviridae and having average case-fatality rate is 30–50% [41, 42].

2.2.1 Mode of transmission

Humans were infected through the bite of ticks, by contact with a CCHF-infected patient during the acute phase of infection, or by contact with secretions, blood or tissues from viraemic livestock. Individuals exposed to ticks

and persons who come in close contact with CCHF patients are include in risk groups [43]. In India it was mainly nosocomial and started with case history of tick bites and close contact with animals during 2011 [43]. The infected *Hyalomma* ticks infested on domestic animals were the main reason for transmission of virus. Once a human was contaminated, the disease was transferred to other close family relatives who go along with the infected individual to hospital, lived in the same house, and attended the funeral of a person who had died due to CCHF, or came in contact with infected body fluids [44].

Ticks of the Hyalomma genus have been reported to be associated with the incidence of the disease and found to play a key role in transmission of CCHFV to mammals [45-48]. High tick activity is associated with warm winters and hot summers. The preponderance of tick species as vectors of CCHFV differs geographically and includes *H. anatolicum* subspecies, which are distributed throughout Eurasia, while in the northern half of Africa *H. marginatum* subspecies predominate. Of the 25 known Hyalomma spp., 15 are important vectors of infectious agents of veterinary and public health importance [49]. Among these, *Hyalomma anatolicum anatolicum* is important, and this species has wide distribution in India [50]. They effectively withstand diverse habitats ranging from warm, arid and semi-arid, harsh lowland, and long dry seasons [49]. *H. anatolicum anatolicum* is known to transmit virus to humans [51].

A transient viraemia in many wild, domesticated and laboratory mammals were caused by CCHFV which having a wide host range. The antibodies against CCHFV have been detected in the sera of variety of animals [52, 53]. Viraemia does not develop in birds however; migratory species could carry infected ticks and play a role in disseminating the virus over long distances [54].

2.2.2 Geographical distribution of CCHFV in India

The geographic distribution of CCHF is closely related to the global distribution of Hyalomma spp. ticks. CCHFV has been reported in over 30 countries covering Africa, South-Eastern Europe, the Middle East and Western Asia [55-57]. India has always been considered at high risk for CCHF, owing to its borders with affected countries such as China and Pakistan. In the 1960, the virus was first isolated from ticks in Pakistan and first reported human case occurred in Rawalpindi in 1976 [58, 59]. An outbreak with 19 cases and 12 deaths was reported from Takhar Province in the northern part of Afghanistan in March 1998 [60]. In Iran, CCHF was first isolated in 1978 and the disease re-emerged in 1999, with high case fatality [61, 62]. In China, CCHF was first isolated in 1965 from a human case and later, in 1984, from *H. asiaticum* ticks from the same region of Xinjiang province in north-western China, which is considered to be the most CCHF-affected area in the country [63].

Until 2011, the existence of CCHF was not known in India, apart from some serological evidence recorded in the past [64]. Serological evidence of the presence of CCHF in India was reported by screening for HI antibodies in animal sera from Jammu and Kashmir, the western border districts, southern regions and Maharashtra state [64, 65]. During December 2010, just prior to the CCHF outbreak, blood samples were collected by NIV, Pune, to examine livestock from abattoirs in the northern adjoining state of Rajasthan and some more distant areas of Maharashtra and West Bengal states [43].

The presence of CCHF disease was confirmed for the first time in India during a nosocomial outbreak, in Ahmadabad district, Gujarat state [43]. After its confirmation in India, sporadic cases of CCHF were reported in

2011–2012 [44]. During the period of 23 June to 25 July 2013, a cluster of suspected VHF cases were reported in Karyana village, Amreli district and, simultaneously, sporadic cases were recorded from Surendra Nagar, Patan district and Kutch district, Gujarat state [44].

2.2.3 Signs and symptoms

The incubation period is 3-7 days. The signs and symptoms may be seen from 5 to 6 days later the direct contact with viraemic livestock or CCHF patients. Typically, the disease pursues a four phase course incubation, pre-haemorrhagic and haemorrhagic phases, and convalescence phase

The CCHF mostly show leukopenia, thrombocytopenia, elevated liver enzymes and prolonged blood coagulation times [42, 43]. High viral load is also associated with a fatal outcome [66]. Approximately 5 to 7 days after the onset of the disease, haemorrhagic manifestations are observed mainly petechiae, epistaxis, haematomas and vaginal bleeding. Death usually occurs between 5 and 7 day of illness. The first phase includes a few days of fever, tiredness, headache and muscle pain, followed by a long asymptomatic period.

After that phase, the first signs that the central nervous system has been start appearing including meningitis, encephalitis and myelitis, which can lead to neurological sequel and in a few cases even death may occurred. Patients with serious illness can show signs of shock or coma, involving neurological symptoms like delirium and convulsions [42, 43]. The haemorrhagic period is short but rapidly progresses and typically begins at the third to fifth day of the illness. Bleeding commonly from the nose, gastrointestinal system, urinary tract, respiratory tract and other sites including the vagina, gingival bleeding, cerebral haemorrhage and bleeding from unexpected sites has been reported.

The convalescence period begins 10–20 days after the onset of disease. It is characterized by labile pulse, tachycardia, temporary complete loss of hair, polyneuritis, difficulty in breathing, poor vision, loss of hearing and loss of memory [66, 67].

2.2.4 Diagnosis

Laboratory diagnosis of the disease is recognized by molecular methods. Indirect immuno-fluorescence assay or ELISA tests are carried out for the detection of IgM and IgG antibodies [68-70]. For the rapid diagnosis of CCHFV infections real-time RT-PCR is the test of choice in the acute phase [42]. The isolation of CCHFV requires a high-containment BSL-4 laboratory. The Gujarat Government has planned to upgrade laboratories to provide CCHF diagnosis, with proper biosafety precautions and handling of these samples, after training and acquisition of all the required biosafety equipment.

2.2.5 Treatment

There is no specific treatment for CCHF. A vaccine based on formalin-inactivated suckling mouse brain, which is not yet approved by the Food and Drug Administration of the USA (FDA) , has been used in Bulgaria and the former Soviet Union [71]. Since no specific treatment is available, supportive treatment includes careful fluid and electrolyte balance, monitoring and replacement with platelets, fresh frozen plasma and erythrocyte preparations [72]. The effect of ribavirin is still controversial but is at present the only antiviral agent with promising effect this drug has not been approved for the treatment of CCHF by the FDA [52, 73, 74]. It was observed that CCHF cases in India supported the use of ribavirin [75].

2.2.6 Prevention and control

2.2.6.1 In the hospital setting

- Isolate the patient in a room that is separate from other patients in the hospital.
- Medical staff handling the patient should wear gloves and a gown, to avoid direct contact with the patient.
- Clinical procedures that are likely to cause spraying of bodily fluids should be avoided, or only performed by medical staff wearing a face shield, or a mask and eye goggles.
- Bleach can be used for disinfection. Alternatively, 5% Lysol may be used.

2.2.6.2 In the family/community setting

- Family members and friends who had direct contact with the patient should be monitored for 14 days, for onset of a febrile illness.

2.2.6.3 Dead body disposal

- Rubber gloves or double surgical gloves should be used for handling the dead body. The persons handling the dead body in hospitals should also wear a mask and use personal protective equipment.
- The dead body should be sprayed with 1:10 liquid bleach. It should then be wrapped with a winding sheet, which is then sprayed with bleach solution.
- The wrapped and bleached body should be placed in a plastic bag, which is then sealed with adhesive tape before transport.
- The ambulance/transport vehicle should also be disinfected after use.

Thus, control measures should be mainly focused on tick control in outbreak areas and on personal protective measures for persons caring for CCHF patients [75-77].

III. DISCUSSION

Vector-borne diseases have emerged as a serious public health problem in countries of the South-East Asia, including India. Many emerging tick born disease have spread globally at the human–animal interface [78]. India has a high-risk area for outbreaks of emerging and new diseases due to the increased population, urbanization, international travel, and change in agricultural practices, environmental factors, change in lifestyle, deforestation, close contact of animals, and a porous international border [79].

Vector-borne diseases now occur in epidemic form on an almost annual basis, causing considerable morbidity and mortality [37]. All these have impact not only on public health but also on the livelihood and economy of affected countries. To deal with this kind of emergency situation a network of laboratories, trained laboratory staff, more high containment diagnostic laboratories, surveillance programmes, modern equipment and trained medical professionals are required. KFD was originally assumed to be limited only to Karnataka state, but there is now evidence of its spread. Similarly, CCHF is not restricted to one district but human positivity has now been recorded in seven districts [44]. To deal with these deadly diseases, strengthening of public health system networking for reporting and circulating information, with participation and education of the general public in the country is required.

IV. CONCLUSION

KFD and CCHF are both of high importance disease and observed almost every year in Karnataka and Gujarat states, respectively. Internationally, KFDV is ranked as one of the highest risk categories of pathogens belonging to Bio Safety Level-4 and has thus serious biosafety concern. Future research priorities for the control of KFD include understanding reasons for the vaccine's low coverage, studying the long-term protection offered by booster doses, and evaluating the appropriateness of the vaccination strategy. Future research also needs to focus on further refining what constitutes a vaccine candidate in order to make the vaccine more effective and avoid the need for periodic boosters. Further, more molecular studies are needed to understand the mechanism of evolution of virulence in KFDV and CCHFV. Such understanding will go a long way towards development of more efficacious KFD vaccines and control of KFD and CCHF disease.

REFERENCES

[1.] D.E. Sonenshine, *Biology of ticks*, Vol 1. New York, Oxford University Press, 1991.

[2.] P. Parola, D. Raoult, Ticks and tickborne bacterial diseases in humans: an emerging infectious threat, *Clin. Infect. Dis, 32*, 2001, 897-928.

[3.] F. Jongejan, G. Uilenberg, The global importance of ticks, *Parasitology, 129(suppl 1),* 2004, S3-S14.

[4.] W.L. Nicholson, K.E. Allen, J.H. McQuiston, E.B. Breitschwerdt, S.E. Little, The increasing recognition of rickettsial pathogens in dogs and people, *Trends Parasitol, 26*, 2010, 205–212.

[5.] J. Piesman, L. Eisen, Prevention of tick-borne diseases, *Annu. Rev. Entomol*, 53, 2008, 323–343.

[6.] D.T. Mourya, P.D. Yadav, V.K. Sandhya, S. Reddy, Spread of Kyasanur Forest disease, Bandipur Tiger Reserve, India, 2012–2013, *Emerg. Infect. Dis, 19*, 2013, 1540-1541.

[7.] P.D. Yadav, Y.K. Gurav, M. Mistry, A.M. Shete, P. Sarkale, A.R. Deoshatwar, et al, Emergence of Crimean-Congo hemorrhagic fever in Amreli District of Gujarat State, India, June to July 2013, *Int. J. Infect. Dis, 18*, 2013, 97-100.

[8.] T.H. Work, H. Trapido, Summary of preliminary report of investigations of the virus research centre on an epidemic disease affecting forest villagers and wild monkeys in Shimoga district, Mysore, *Indian J. Med. Sci, 11*, 1957, 340–341.

[9.] T.H. Work, H. Trapido, D.P. N.M. L. Rao, P.N. Bhatt, K.G. Kulkarni, Kyasanur Forest Disease III: A preliminary report on the nature of the infection and clinical manifestations in human beings, *Indian J Med Sci, 11*, 1957, 619–645.

[10.] H. Trapido, P.K. Rajagopalan, T.H. Work, M.G. Varma, Kyasanur Forest disease, VIII. Isolation of Kyasanur forest disease virus from naturally infected ticks of the genus Haemaphysalis, *Indian J Med Res, 47,* 1959, 133-138.

[11.] G. Geevarghese, A.C. Mishra, *Haemaphysalis ticks of India*, 1st Edition. Elsevier Pub, 2011.

[12.] H. Trapido, Kyasanur Forest disease: a new infection of man and monkeys in tropical India by a virus of the Russian spring summer-complex, *Proceedings of the Ninth Pacific Science Congress, 17,* 1957, 80-84.

[13.] T.H. Work, F.M. Roderiguez, P.N. Bhatt, Virological epidemiology of the 1958 epidemic of Kyasanur Forest disease, *Am. J. Public Health Nations Health, 49,* 1959, 869-874.

[14.] G. Dobler, Zoonotic tick–borne flaviviruses, *Vet Microbiol, 140,* 2010, 221–228.

[15.] P. Pattnaik, Kyasanur forest disease: An epidemiological view in India, *Rev. Med. Virol, 16(3),* 2006, 151-165.

[16.] M.A. Sreenivasan, H.R. Bhat, P.K. Rajagopalan, The epizootics of Kyasanur Forest disease in wild monkeys during 1964 to 1973, *Trans. R. Soc. Trop. Med. Hyg, 80(5),* 1986, 810-814.

[17.] G.S. Kasabi, M.V. Murhekar, P.D. Yadav, R. Raghunandan, S.K. Kiran, V.K. Sandhya et al, Kyasanur Forest disease, India, 2011–2012, *Emerg. Infect. Dis,19,* 2013, 278–282.

[18.] D.T. Mourya, P.D. Yadav, R. Mehla, P.V. Barde, P.N. Yergolkar, J.P. Thakare et al, Diagnosis of Kyasanur Forest disease by nested RT-PCR, real-time RT-PCR and IgM capture ELISA, *J Virol Methods, 186,* 2012, 49–54.

[19.] P.V. Shiji, V. Viswanath, S. Sreekumar, R. Sreejith, A. Majeed, V. Udayabhaskaran, Kyasanur Forest Disease- First Reported Case in Kerala, *Journal of Association of Physicians of India, 64,* 2016, 90-91.

[20.] J.K. Sarkar, S.N. Chatterjee, Survey of antibodies against arthropod–borne viruses in the human sera collected from Calcutta and other areas of West Bengal, *Ind. J. Med. Res, 50,* 1962, 833-841.

[21.] K. Banerjee, *Kyasanur forest disease*, In: Monath TP, editor. Arbovirus epidemiology and ecology. Boca Raton (FL): CRC Press, 1988. Pp 93-116.

[22.] G. Grard, G. Moureau, R.N. Charrel, J.J. Lemasson, J.P. Gonzalez, P. Gallian, T.S. Gritsun et al., Genetic characterization of tick–borne flaviviruses: new insights into evolution, pathogenetic determinants and taxonomy, *Virology, 361(1),* 2007, 80–92.

[23.] C.G. Iyer, Rao L.R, Work TH, DP Narasimha Murthy, Kyasanur Forest Disease VI. Pathological findings in three fatal human cases of Kyasanur Forest Disease, *Indian J. Med. Sci, 13,* 1959, 1011-1022.

[24.] P.M.R. Adhikari, M.G.Prabhu, C.V. Raghuveer, M. Bai, M.A. Mala, Clinical study of 100 cases of Kyasanur Forest disease with clinic-pathological correlation, *Indian J. Med. Res, 47(5),* 1993, 124-130.

[25.] D.L. Heymann, *An Official Report of the American Public Health Association,* In D. L. Heymann (Ed.), Control of Communicable Diseases Manual, (18th ed) Washington, D.C. American Public Health Association, 2004, 35 –37.

[26.] K. Pavri, Clinical, clinicopathologic, and hematologic features of Kyasanur forest disease, *Rev. Infect. Dis, 11,* 1989, 854.

[27.] S. Upadhyaya, D.P. Murthy, Kyasanur Forest Disease virus neutralizing antibodies in human sera in Mysore State, *Indian J. Med. Res, 55(2),* 1967, 103-108.

[28.] R. Mehla, S.R.P. Kumar, P. Yadav, P.V. Barde, P.N. Yergolkar, B.R. Erickson et al., Recent Ancestry of Kyasanur Forest Disease Virus, *Emerg. Infect. Dis, 15(9),* 2009, 1431-1437.

[29.] J. Wang, H. Zhang, S. Fu, H. Wang, D. Ni, R. Nasci, Isolation of Kyasanur forest disease virus from febrile patient, Yunnan, China, *Emerg. Infect. Dis, 15,* 2009, 326-328.

[30.] I.M. Mackay, K.E. Arden, A. Nitsche, Real–time PCR in virology, *Nuc Acids Res, 30,* 2002, 1292-1305.

[31.] Z.A. Eldadah, D.M. Asher, M.S. Godec, K.L. Pomeroy, L.G. Goldfarb, S.M. Feinstone et al, Detection of flaviviruses by reverse–transcriptase polymerase chain reaction, *J. Med. Virol, 33,* 1991, 260-267.

[32.] M. Tanaka, Rapid identification of flavivirus using the polymerase chain reaction, *J. Virol. Methods, 41,* 1993, 311–322.

[33.] P.V. Fulmali, Priorities and future of diagnosis of emerging viral diseases, *Health Sciences, 1(1),* 2012.

[34.] CDC, Kyasanur Forest disease, 2013, Available at: http://www.cdc.gov/vhf/kyasanur, Accessed on June 2015.

[35.] K. Dhama, R. Tiwari, S. Chakraborty, A. Kumar, M. Karikalan, R. Singh, R.B. Rai, Global warming and emerging infectious diseases of animals and humans: current scenario, challenges, solutions and future perspectives – a review, *Int. J. Curr. Res, 5(7),* 2013a, 1942–1958.

[36.] S. Ghosh, P. Azhahianambi, J. Fuente, *Control of ticks of ruminants, with special emphasis on livestock farming systems in India*: present and future possibilities for integrated control—a review, Experiment. Appl. Acarol, 40, 2006, 49 – 66.

[37.] A.M. Kilpatrick, S.E. Randolph, Drivers, dynamics, and control of emerging vector-borne zoonotic diseases, *Lancet, 380(9857),* 2012, 1946-1955.

[38.] S. Jaureguiberry, P. Tattevin, A. Tarantola, F. Legay, A. Tall, P. Nabeth et al, Imported Crimean-Congo hemorrhagic fever, *J. Clin. Microbiol, 43,* 2005, 4905-4907.

[39.] D.I. Simpson, E.M. Knight, G. Courtois, M.C. Williams, M.P. Weinbren, J.W. Kibukamusoke, Congo virus: a hitherto undescribed virus occurring in Africa I. Human isolations-clinical notes, *East Afr. Med. J, 44,* 1979, 86–92.

[40.] M. Williams, P.M. Tukei, M. Lule, E. Mujomba, A. Mukuye, Virology: identification studies, *Rep. E. Afr. Virus Res. Inst, 16,* 1966, 24–26.

[41.] M.P. Chumakov, A.M. Butenko, N.V. Shalunova, L.I. Martyanova, W.E. Smirnova, V.N. Bashkirtsev et al, New data on the virus causing Crimean hemorrhagic fever (CHF), *VoprVirusol, 3,* 1968, 377.

[42.] O. Ergonul, Crimean-Congo haemorrhagic fever, *Lancet Infect Dis, 6,* 2006 203–214.

[43.] D.T. Mourya, P.D. Yadav, A.M. Shete, Y.K. Gurav, C.G. Raut, R.S. Jadi et al, Detection, isolation and confirmation of Crimean-Congo hemorrhagic fever virus in human, ticks and animals in Ahmadabad, India, 2010–2011, *PLoS. Negl. Trop. Dis, 6,* 2012, 1653.

[44.] P.D. Yadav, C.G. Raut, D.T. Mourya, Re-occurrence of Crimean-Congo haemorrhagic fever in Ahmedabad, Gujarat, India (2012): a fatal case report, *Indian J Med Res, 138,* 2013, 1027-1028.

[45.] S.W. Gordon, K.J. Linthicum, J.R. Moulton, Transmission of CrimeanCongo hemorrhagic fever virus in two species of Hyalomma ticks from infected adults to co feeding immature forms, *Am. J. Trop. Med. Hyg, 48,* 1993, 576–580.

[46.] H.G. Zeller, J.P. Cornet, J.L. Camicas, Experimental transmission of Crimean-Congo hemorrhagic fever virus by west African wild groundfeeding birds to Hyalomma marginatum rufipes ticks, *Am. J. Trop. Med. Hyg, 50,* 1994, 676–681.

[47.] T.M. Logan, K.J. Linthicum, C.L. Bailey, D.M. Watts, J.R. Moulton, Experimental transmission of Crimean-Congo hemorrhagic fever virus by Hyalomma truncatum Koch, *Am. J. Trop. Med. Hyg*, *40*, 1989, 207-212.

[48.] D.J. Dohm, T.M. Logan, K.J. Linthicum, C.A. Rossi, M.J Turell, Transmission of Crimean-Congo hemorrhagic fever virus by Hyalomma impeltatum (Acari:Ixodidae) after experimental infection, *J. Med. Entomol, 33,* 1996, 848–851.

[49.] M.A. Bakheit, A.A. Latif, Z. Vatansever, U. Seitzer, J. Ahmed, *The huge risks due to hyalomma ticks* In: Arthropods as vectors of emerging diseases. Heinz Mehlhorn. Ed. Springer publication. pp.168.

[50.] A.A. Latif, Tick (Acari: Ixodoidea: Ixodidae) immature feeding on cattle, camels and sheep in the Sudan, with notes on behaviour of Hyalomma anatolicum anatolicum larvae fed on different hosts, Insect Sci. Applicat, 6, 1985, 59–61.

[51.] R. Vorou, I.N. Pierroutsakos, H.C. Maltezou, Crimean-Congo hemorrhagic fever, *Curr. Opin. Infect. Dis, 20,* 2007, 495–500.

[52.] A.J. Shepherd, P.A. Leman, R. Swanepoel, Viremia and antibody response of small African and laboratory animals to Crimean-Congo hemorrhagic fever virus infection, *Am. J. Trop. Med. Hyg*, *40*, 1989, 541–547.

[53.] A.M. Palomar, A. Portillo, P. Santibanez, D. Mazuelas, J. Arizaga et al, Crimean-Congo hemorrhagic fever virus in ticks from migratory birds, Morocco, *Emerg. Infect. Dis, 19,* 2013, 260-263.

[54.] A.C. Mishra, M. Mehta, D.T. Mourya, S. Gandhi, Crimean–Congo haemorrhagic fever in India, *Lancet, 378,* 2011, 372.

[55.] R. Flick, C.A. Whitehouse, Crimean-Congo hemorrhagic fever virus, *Curr Mol Med, 5,* 2005, 753–760.

[56.] F. Tahmasebia, S.M. Ghiasib, E. Mostafavib, M. Moradib, N. Piazakc, A. Mozafarid et al, Molecular epidemiology of Crimean- Congo hemorrhagic fever virus genome isolated from ticks of Hamadan province of Iran, *J Vector Borne Dis, 47,* 2010, 211–216.

[57.] S. Olschlager, M. Gabriel, J. Schmidt-Chanasit, M. Meyer, E. Osborn, N.G. Conger et al, Complete sequence and phylogenetic characterization of Crimean-Congo hemor- rhagic fever virus from Afghanistan, *J Clin Virol, 50,* 2011, 90–92.

[58.] M.I. Burney, A. Ghafoor, M. Saleen, P.A. Webb, J. Casals, Nosocomial outbreak of viral hemorrhagic fever caused by Crimean hemorrhagic fever-Congo virus in Pakistan, January 1976, *Am J Trop Med Hyg, 29,* 1980, 941-947.

[59.] S. Junaid, U. Muhammad, A. Nadeem, S.A. Sethi, S. Muhammad, Crimean–Congo hemorrhagic fever: a first case from Abbottabad, Pakistan, International. *Journal of Infectious diseases, 13(3),* 2009, 121-123.

[60.] M.R. Wallace, B.R. Hale, G.C. Utz, P.E. Olson, K.C. Earhart, S.A. Thornton et al, Endemic infectious diseases of Afghanistan, *Clin Infect Dis, 34(suppl 5),* 2002, 171–207.

[61.] P. Sureau, J.M. Klein, J. Casals, Isolation of Thogoto, wad medani, wanowrie, and Crimean-Congo hemorrhagic fever viruses from ticks of domestic animals in Iran, *Ann Virol (Inst Pasteur), 131,* 1980, 185–200.

[62.] S. Izadi, K. Holakouie-Naieni, S.R. Majdzadeh, S. Chinikar, A. Nadim, F. Rakhshaniet al, Seroprevalence of Crimean-Congo hemorrhagic fever in Sistan-va-Baluchestan province of Iran, *Japan J Infect Dis, 59(5),* 2006, 326-328.

[63.] Q. Tang, C. Prehaud, M. Bouloy, F. Conghui, Z. Xiuqing, C. Huaxin, Sequencing and analysis of S gene segment of XHFV, *Chin J Microbiol Immunol, 19,* 1999, 461–465.

[64.] F.M. Rodrigues, V.S. Padbidri, G.R. Ghalsasi, N.P. Gupta, V.B. Mandke, Prevalence of crimean haemorrhagic-Congo virus in Jammu and Kashmir State, *Indian J Med Res, 84,* 1986, 134–138.

[65.] J. Shanmugam, S.E. Smirnova, M.P. Chumakov, Presence of antibodies to arboviruses of the Crimean haemorrhagic fever Congo (CHF-Congo) group in human being and domestic animals in India, *Indian J Med Res, 64,* 1976, 1403–1413.

[66.] D.M. Watts, T.G. Ksiasek, K.J. Linthicum, H. Hoogstraal, *CrimeanCongo hemorrhagic fever*, In: Monath TP. Editor, The arboviruses: epidemiology and ecology, Boca Raton, FL: CRC Press, 1988.

[67.] R. Swanepoel, D.E. Gill, AJ Shepherd, P.A. Leman, J.H. Mynhardt, S. Harvey, The clinical pathology of Crimean-Congo hemorrhagic fever, *Rev Infect Dis,11(Suppl 4),* 1989, 794–800.

[68.] A.J. Shepherd, R. Swanepoel, D.E. Gill, Evaluation of enzyme-linked immunosorbent assay and reversed passive hemagglutination for detection of Crimean-Congo hemorrhagic fever virus antigen, *J. Clin. Microbiol, 26,* 1988, 347–353.

[69.] F.J. Burt, P.A. Leman, J.C., R. Abbott, Swanepoel, Serodiagnosis of CrimeanCongo haemorrhagic fever, *Epidemiol Infect, 113,* 1994, 551-562.

[70.] C. Drosten, B.M. Kummerer, H. Schmitz, S. Gunther, Molecular diagnostics of viral hemorrhagic fevers, *Antiviral Res, 57,* 2003, 61-87.

[71.] M. Mardani, M.K. Jahromi, K.H. Naieni, M. Zeinali, The efficacy of oral ribavirin in the treatment of Crimean-Congo hemorrhagic fever in Iran, *Clin. Infect. Dis, 36,* 2003, 1613–1618.

[72.] S.P. Fisher-Hoch, J.A. Khan, S. Rehman, S. Mirza, M. Khurshid, J.B. Mc Cormick, Crimean- Congo hemorrhagic fever treated with oral ribavirin, *Lancet, 346,* 1995, 472–475.

[73.] G.H. Tignor, C.A. Hanham, Ribavirin efficacy in an in vivo model of Crimean-Congo hemorrhagic fever virus (CCHF) infection, *Antiviral Res, 22,* 1993, 309–325.

[74.] D.M. Watts, M.A. Ussery, D. Nash, C.J. Peters, Inhibition of CrimeanCongo hemorrhagic fever viral infectivity yields in vitro by ribavirin, *Am. J. Trop. Med. Hyg, 41,* 1989, 581–585.

[75.] A.K. Patel, K.K. Patel, M. Mehta, T.M. Parikh, H. Toshniwal, K. Patel, First Crimean-Congo hemorrhagic fever outbreak in India, *J Assoc Physicians India, 59,* 2011, 585–589.

[76.] C.E. Schreck, E.L. Snoddy, A. Spielman, Pressurized sprays of permethrin or deet on military clothing for personal protection against Ixodes dammini (Acari: Ixodidae), *J. Med. Entomol, 23,* 1986, 396–399.

[77.] O. Ergonul, C.A. Whitehouse, *Risk groups and control measures for crimean-congo hemorrhagic fever*, In: Ergonul O, Whitehouse CA. Editors, Crimean-Congo hemorrhagic fever: a global perspective, Dordrecht: Springer, 2007, pp. 273-280.

[78.] M. Greger, The human/animal interface: emergence and resurgence of zoonotic infectious diseases. *Crit. Rev. Microbiol*, *33*, 2007, 243–299.

[79.] V. Wiwanitkit, M.Y. Singh, *Emerging infectious diseases in India*, New York: Nova Science Publishers, 2009.