

Crimean-Congo Hemorrhagic Fever: Current Scenario in India

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Abstract India is considered as a hot spot for emerging infectious diseases. In the recent past many infectious diseases of emerging and re-emerging nature have entered this subcontinent and affected a large number of populations. A few examples are Nipah, Avian influenza, Pandemic influenza, severe acute respiratory syndrome corona virus and Chikungunya virus. These diseases have not only affected human and animal health but also economy of the country on a very large scale. During December 2010, National Institute of Virology, Pune detected Crimean-Congo hemorrhagic fever virus specific IgG antibodies in livestock serum samples from Gujarat and Rajasthan states. Subsequently, during January 2011 Crimean-Congo hemorrhagic fever virus was confirmed in a nosocomial outbreak, in Ahmadabad, Gujarat, India. Retrospective investigation of suspected human samples confirmed that the virus was present in Gujarat state, earlier to this outbreak. This disease has a case fatality rate ranging from 5 to 80 %. Earlier presence of hemagglutination inhibition antibodies have been detected in animal sera from Jammu and Kashmir, the western border districts, southern regions and Maharashtra state of India. The evidences of virus activity and antibodies were observed during and after the outbreak in human beings, ticks and domestic animals (buffalo, cattle, goat and sheep) from Gujarat State of India. During the year 2012, this virus was again reported in human beings and animals. Phylogenetic analysis

showed that all the four isolates of 2011, as well as the S segment from specimen of 2010 and 2012 were highly conserved and clustered together in the Asian/Middle East genotype IV. The S segment of South-Asia 2 type was closest to a Tajikistan strain TADJ/HU8966 of 1990. The present scenario in India suggests the need to look seriously into various important aspects of this zoonotic disease, which includes diagnosis, intervention, patient management, control of laboratory acquired and nosocomial infection, tick control, livestock survey and this, should be done in priority before it further spreads to other states. Being a high risk group pathogen, diagnosis is a major concern in India where only a few Biosafety level 3 laboratories exist and it needs to be addressed immediately before this disease becomes endemic in India.

Keywords Crimean-Congo hemorrhagic fever · Outbreak · Ticks · Polymerase chain reaction · Human beings · Animals · India

Introduction

The Crimean-Congo hemorrhagic fever (CCHF) was first characterized in the West Crimean region of the former Soviet Union in 1944 during a large outbreak and was isolated in 1956 from a patient [1–4]. The virion is spherical, ~90–100 nm in diameter and is in the form of enveloped particles with a tripartite, single-stranded RNA genome having negative polarity. This virus belongs to the genus *Nairovirus* in the family Bunyaviridae and causes fatal viral hemorrhagic fever (VHF) in humans, with a reported high mortality rate [5]. The genus *Nairovirus* includes 34 described viruses, which are placed in seven serogroups based on the antigenic relatedness. The

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groupings have subsequently been sustained through demonstration of morphological and phylogenetic relatedness. Only three viruses of this genus are known to cause human disease: they are CCHFV, Dugbe and Nairobi sheep disease virus [6]. In India, among NSD group, Ganjam virus is considered a variant of NSDV. Ganjam virus, also known to cause human infection, is transmitted through *Hyalomma* species of ticks. The antibodies against this virus have been recorded in animals and humans [7–11]. CCHF virus has tri-partite genome segments; small (S), medium (M) and large (L), which encode for the nucleocapsid protein (NP), the envelope glycoproteins G1 and G2 and an RNA dependent RNA polymerase respectively [12–14].

CCHF infections have been found in parts of Africa, Asia, Eastern Europe and the Middle East [15–21]. Among the tick-borne hemorrhagic viruses CCHFV has an extensive geographic range [22]. In nature, humans get infected either through a tick bite or by contact with an acute phase CCHF patient or by contact with blood or tissues from viremic livestock [4]. This review elucidates the current scenario including presence of this virus in India, consequences on public health, issues with diagnostic system, surveillance program to monitor this disease, network of laboratories, and requirement of infrastructure to address CCHF outbreaks.

The review was prepared after an extensive search for literature on VHF and CCHF using different online web pages including Pubmed, World Health Organization (WHO) and Centre for Disease Control and Prevention (CDC). All the recent literature published on CCHFV from India was thoroughly studied and also epidemiological data from the National Institute of Virology (NIV), Pune, India was considered while compiling this review.

Geographical Distribution and Spread of CCHF Virus in India

Since the discovery of CCHF virus, nearly 140 outbreaks involving more than 5,000 cases have been reported all over the world from almost 52 countries [23]. The known distribution of CCHF virus covers the greatest geographic range as compared to any other tick-borne virus. There are reports of viral isolation and/or disease in Africa, Asia, southeast Europe and the Middle East [15–21]. The average case fatality rate is 30–50 %, but variable mortality rates from 5 to 80 % have been reported in various outbreaks. The mortality rate is higher with nosocomial infections than through tick bites which may be related to the virus dose [24].

India has been considered as a hot spot for many emerging and re-emerging infectious diseases [25]. There has been suspicion of CCHFV presence in India due to confirmed CCHF positive cases in adjoining countries like

Pakistan, China, and Afghanistan [11, 26]. India has an ancient history with these countries and also trade records of livestock and human movements. The presence of this virus in India raised high suspicion, when it was isolated from the tick species *Hyalomma anatolicum* and also from a mixture of *Hyalomma* and *Boophilus* species collected in Pakistan [27]. In 1973, Shanmugam et al. [28], tested a total of 643 human sera from all over India. Of these, nine samples from Kerala and Pondicherry were found positive for CCHF virus specific antibody. In the same study, 34 out of 655 serum samples, collected from sheep, horse, goat and other domestic animals from all over India showed evidence of CCHFV antibodies. Most of the positive sera in southern India were collected from goats. Evidence of hemagglutination inhibition antibody positivity was recorded in the animal sera tested during a serosurvey conducted in Jammu and Kashmir and in the western border districts of India in 1976. In the same study antibodies were also detected in domestic animal sera from different states/territories of southern India and from Maharashtra state. Mainly goat serum samples from South India were found to be positive [29]. Subsequently, in 1977, Kaul et al. [30], conducted a survey of *Ixodid* ticks to determine the CCHFV activity in Jammu and Kashmir State, India, but CCHFV isolation was not obtained from 138 pools comprising eight species under six genera of ticks. All these studies were based only on serological findings in which no virus isolation could be achieved and hence no clear evidence of this virus could be obtained. During December 2010, just prior to CCHF outbreak, blood samples were collected by the NIV, Pune to examine livestock for the presence of CCHFV specific IgG antibodies from abattoirs in the northern adjoining state of Rajasthan and some more distant areas of Maharashtra and West Bengal. The serum samples of buffalo, goat and sheep from Sirohi district, in southern Rajasthan were found positive for IgG antibodies against CCHFV. In January 2011, cases with hemorrhagic manifestations among hospital staff were reported from Ahmadabad of Gujarat State, India. Out of 86 samples screened, one hospital and one family contact (both asymptomatic) were positive for the presence of IgM antibodies against CCHFV and three CCHF positive cases showed high titer of IgM antibodies [31]. Speculation was made that higher number of suspected cases were present in Gujarat State [32]. Animal serum samples from northern West Bengal and Pune district of Maharashtra were negative for CCHFV IgG antibodies. Evidence of CCHFV infection (IgG positive) was also found in a follow-up study of livestock (buffalo, cattle, goat, and sheep) from Kolkata and the surrounding villages of Changodar, Jivanpara and Navapura. Overall it was observed that IgG antibody positivity in small sample sizes varied between villages (10–43 %) [31].

Phylogenetic and Ancestral Relationship of Indian CCHF Virus

Earlier phylogenetic studies based on complete S genome segment sequences showed that CCHFV strains cluster in seven distinct groups while molecular epidemiology of 70 CCHFV isolates (based on “S” segment) have revealed the three groups of genetically related isolates; Group A (African clade and Asian clade comprising isolates from, China, Iran, Russia and Madagascar), Group B (South and West Africa and Iran) and Group C (Greece) [33, 34]. Recent, S segment analysis had shown that CCHFV strains cluster in six to seven distinct groups as West-Africa in group I, Central Africa in group II, South-Africa and West Africa in group III, Middle-East and Asia in group IV, Europe in group V and Greece in group VI. The group IV may split into two distinct groups, Asia 1 and Asia 2. Complete genome analysis of CCHFV isolates not only revealed high genetic diversity but also showed recombination and re-assortment which resulted in more complicated evolutionary routes of the virus, than a mutation-based selective forces [33–37]. Earlier data on serological testing has suggested that there are very few significant differences among strains of CCHFV at different geographic locations. However, more recent data based on nucleic acid sequence analysis have revealed the extensive genetic diversity [38].

Sequence-based molecular characterization of the Indian CCHFV showed that they possess the functional motifs, known to occur in the S, M and L gene segment products as in other CCHFV. Phylogenetic analysis showed that all the four isolates of 2011, as well as the S segment from isolates of 2010 were highly conserved and clustered together in the Asian/Middle East genotype IV. The S segment of South-Asia 2 type was closest to a Tajikistan strain TADJ/HU8966 of 1990 (98.5 % nucleotide identity) while the M segment was closest to type M2. Both M and L segments were closest to an Afghanistan strain Afg09-2990 of 2009 (93 and 98 % nucleotide identity respectively). Thus, the Indian isolates were identified as a South-Asia 2/M2 far-east virus combination and the differing parental origin in the S and L/M segments suggested that it might be an intra-genotypic reassortant. The molecular clock studies further revealed that the ancestry of these viruses was not very recent and dated back to about 33 years on the basis of the S segment, whereas it was about 15 years based on the M segment. However, the 2011 outbreak may not have resulted from a very recent introduction. Considering this, so far there was no evidence which confirmed multiple circulating strains in the country. The CCHFV sequences of human case from 2012 showed similarity with CCHFV sequences of year 2010 and 2011, reported from India, which indicates that same virus strain was in the circulation

(NIV, unpublished data). Subsequently, the possibility of a recent re-introduction of the virus from any of the neighboring countries cannot be ruled out [39].

Maintenance of CCHF Virus Cycle in Host and Vector

This virus circulates in the nature in an “enzootic tick–vertebrate–tick” cycle and there is no evidence that the virus causes disease in any animal other than newborn laboratory mice. CCHFV infection has been demonstrated more commonly among smaller wildlife species such as hares and hedgehogs that act as hosts for the immature stages of the tick vectors [40]. CCHFV has been isolated from numerous domestic and wild vertebrates; cattle, goats, sheep, hares, hedgehogs, a *Mastomys* spp. of mouse and even antibodies against CCHFV have been detected in the sera of domestic animals [41–44]. Large herbivores have the highest seroprevalence rate for CCHFV [45]. Seroprevalence rates of 13–36 % have been reported in some studies, while others suggest that more than 50 % of adult livestock in endemic regions have antibodies against the virus. CCHFV infections are asymptomatic in animals other than experimentally inoculated newborn rodents (laboratory mice, rats and Syrian hamsters) [46]. The potential roles of migratory birds and the movement of livestock carrying ticks in the spread of the virus over distant geographical areas have been described. Although birds carry CCHF infected ticks, they don’t show presence of the virus or CCHFV specific antibodies [11, 47].

CCHF virus has been detected in at least 31 species of ticks, from seven genera of the family Ixodidae (hard ticks). However, members of the genus *Hyalomma* seem to be the principal vector. Transovarial, transstadial and venereal transmission of the virus occurs in this genus. CCHFV has been reported from a biting midge (*Culicoides* spp.) and also been found in two species of *Argasidae* (soft ticks). However, experimental infections suggest that this virus does not replicate in this family of ticks and even in other several species of ticks [14, 48–52].

CCHFV specific IgG antibodies were detected in cattle, goat and buffalo from surrounding villages of the Ahmadabad city in Gujarat state, India and virus was isolated from the pool of male *Hyalomma anatolicum anatolicum* ticks, collected from a buffalo in the affected area, which suggested that this disease was not due to the recent introduction of CCHFV to this area [31]. *Ornithodoros* tick pool was found positive for CCHFV by RT-PCR in routine screening after the outbreak from Ahmadabad, Gujarat State (unpublished data NIV, Pune). Rodent’s serum samples screened from the affected area by real time RT-PCR were found negative. During the 2011 Gujarat outbreak, follow-up studies revealed that sheep, goats, buffalo were the main hosts for CCHFV, in which not only IgG

antibodies but viral RNA was also detected in serum samples [31].

Clinical Features of Typical CCHF Patient

Humans appear to be the only host of CCHFV in which the disease is manifested. Clinical progress of CCHF differs from mild to moderate or severe. Initial symptoms of CCHF differ from patient to patient. The typical course of CCHF shows that the disease progresses through four distinct phases, i.e., incubation, pre-hemorrhagic, hemorrhagic and convalescence [29]. The clinical features observed commonly in CCHF patients from India were high grade fever, headache, body ache, nausea, vomiting, abdominal pain, dizziness, malaise, photophobia, diarrhea, petechiae, ecchymosis and visceral bleeding. Bleeding from other sites including the vagina has also been reported in the very severe cases [15, 34, 53]. The common laboratory findings of CCHF patients who died due to this infection from India demonstrated elevated prothrombin time (PT) and activated partial thromboplastin time (aPTT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic dehydrogenase (LDH), creatinine phosphokinase (CPK), leucopenia and thrombocytopenia [15, 53, 54]. It has been found that in some patients CCHF develops into a serious or fatal disease while in others it is only mild or asymptomatic but in India most of the cases showed severe manifestations [54, 55]. One of the major reasons for nosocomial infection of CCHF could be the high viral load which helps in virus dissemination [56]. In severe cases, hemorrhagic manifestations develop within 3–6 days after onset of disease. Hence, it becomes imperative to provide a differential diagnosis for CCHF with respect to other viral diseases mimicking the similar signs and symptoms which will be helpful in early treatment of affected patients. The pathogenesis of CCHF is not well understood due to the limited number of Biosafety level-4 (BSL-4) laboratories and unavailability of proper animal model. However, a common pathogenic feature of viruses causing VHF is their ability to disable the host immune response by attacking and manipulating the cells that initiate the antiviral response [57].

Diagnostic Capacity in India

Early diagnosis of CCHF is critical for the management of patients, to prevent the transmission of the disease to the community and potential nosocomial infections. The differential diagnosis of CCHF differs depending on that particular geographic region. In India, overlapping symptoms of hemorrhagic fevers like dengue, Kyasanur forest disease, Hantavirus hemorrhagic fever and other diseases

(Malaria, meningococcal infections and leptospirosis) are of major concern in CCHF diagnosis [58]. The diagnosis of VHF is mainly based on typical clinical presentation and thereafter confirmed by detection of either virus or viral RNA or by demonstration of a rise of antibody titers against it [59]. Laboratory diagnosis of CCHFV includes the reverse transcription polymerase chain reaction (RT-PCR) and real-time RT-PCR assay, which is the method of choice for the rapid detection of viral RNA in the acute phase, considered highly specific, sensitive and rapid [60–62]. The consumables and instrumentation required for these techniques are cost expensive and out of the financial reach of many local laboratories. This can delay the timely diagnosis and in turn early management of patients. Detection of immunoglobulin M (IgM) during the acute phase and immunoglobulin G (IgG) antibodies in convalescent phase sera is detectable by enzyme-linked immunosorbent assay (ELISA) and immunofluorescent antibody (IFA) [63, 64]. Patients with fatal disease as well as patients in the first few days of illness do not usually develop a measurable antibody (IgM) response and in these individuals diagnosis is achieved either by virus detection in blood, serum, plasma, urine or tissue samples using molecular techniques.

Diagnosis of suspected CCHF sample is strictly performed in specially-equipped, high Biosafety level laboratories. In India, NIV, Pune and High Security Animal Disease Laboratory (HSADL), Bhopal are the only two laboratories which have the capacity to provide diagnosis on CCHF virus. The National Institute of Communicable Diseases (NICD) also played a major role in outbreak investigations of communicable diseases and was involved in the early phase of CCHF investigations. The NIV is India's premier virology research institute and is identified as the WHO Collaborating Center for arboviruses reference and hemorrhagic fever reference and research. It has functional state of the art BSL-3 laboratory to provide diagnosis on highly infectious pathogens and also has a newly constructed BSL-4 laboratory. During the first outbreak of CCHF in Gujarat state of India, all the human samples were sent to the NIV, Pune for diagnosis of suspected samples. The laboratory provided the diagnosis using ELISA, and/or molecular methods and also isolated CCHF virus. The entire CCHF diagnostic assays have been thoroughly validated and standardized approach has been followed in the laboratory to provide a correct diagnosis on CCHF. Quick and accurate diagnosis were provided to ensure early patient management.

The HSADL is one of the premier facility recognized by Office International des Epizooties (OIE) (the world's apex organization for Animal Health for handling exotic and emerging pathogens of animals) by virtue of its BSL-4 containment laboratory and animal experimentation facility. The real-time RT-PCR assay for diagnosis of CCHFV

has been standardized and validated. During CCHF outbreak around 250 veterinary samples were sent to the HSADL for surveillance of CCHF in domestic animals. Both of these laboratories have the independent capacity to provide CCHF diagnosis as they have specialized laboratories with appropriate facilities and expertise. The process, system and test method used for diagnosis are consistently validated for quality assurance. These laboratories are accredited internationally which assures the clinician and the patients that the test reports are reliable and also gives a feedback to the laboratory on its performance as per international standards. As this virus belongs to risk group-4, there are limitations for diagnosing CCHF in several affected areas. Also there is high risk involved in the infectious sample collection and transportation to diagnostic laboratories which are important issues that needs to be addressed by hospitals or any agency involved in it. At the source while collecting samples in outbreak scenario, personal protection equipment, packing of samples should be performed as per international guidelines described by WHO and CDC [65, 66]. To cope up with all these problems, diagnostic capacities for CCHF should be increased mainly in affected areas. Also a national network of local, state, public health, hospital-based and veterinary laboratories should be developed which will respond to the public health emergencies and provide laboratory diagnostics on CCHF.

Treatment Protocol in India

After an outbreak of CCHF in Gujarat state of India during 2011, Directorate General of Health Services, Ministry Of Health and Family Welfare, Government of India issued a protocol for treatment of CCHF in India [67]. As per the protocol the patients are categorized into three types as follows.

- I. Category-A: These patients have relatively mild disease (fever <38.5 °C, No systemic bleeding, Alanine Transaminase (SGPT) levels <150 IU, Platelet count $>50,000$). These patients improve spontaneously in about day 10 of illness. The patient can be managed with supporting therapy and regular monitoring for worsening of symptoms.
- II. Category-B: These patients are in the first 5 days of illness and are severely ill with high grade fever (>38.5 °C), local and systemic bleeding manifestations, having Alanine Transaminase (SGPT) levels of 150 IU or more, aspartate aminotransferase (SGOT) of 200 IU or more, platelets ($<50,000$) or aPTT of 60 s or more.
- III. Category-C: These patients first seen/recognized as CCHF after day 5 and are in a terminal state with

disseminated intravascular coagulation and multi organ failure. Treatment with ribavirin is indicated but the prognosis is very poor. Because the effectiveness of ribavirin is controversial, usage of ribavirin for the treatment of CCHF should be left to the decision of physician and patient.

Supportive care is necessary based on the patient's physiologic condition. Because most patients requiring pre-hospital evaluation and transport are in the early stages of the disease, universal precautions should be adequate. In patients with respiratory symptoms, use of face shields and high-efficiency particulate air (HEPA) filter masks should be compulsory.

General supportive therapy is the mainstay of patient management in CCHF. Intensive monitoring to guide volume and blood component replacement is required. Supportive care includes fluid management by intravenous crystalloids, oxygen, cardiac monitoring and administer blood and blood products as clinically indicated. Intramuscular injections and the use of aspirin or other anticoagulants should be avoided. Invasive procedures should be minimized because of the risk associated with viral transmission from sharp objects. There is currently no specific antiviral therapy for CCHF. However, the antiviral drug ribavirin has been found effective against the CCHFV in vitro, although its exact mechanism of action against this virus is unclear. Although its clinical use in CCHF treatment is controversial, it is the only antiviral drug currently available [68–70]. However the benefits of ribavirin treatment have not been examined under the strict conditions of a randomized clinical trial and the drug is not approved for the treatment of CCHF by the US Food and Drug Administration [71]. Ribavirin therapy was found to be effective in CCHF patient when administered in the early phase of illness during CCHF outbreak in Gujarat [54]. The optimal route of administration of ribavirin is by mouth preferably taken with food. During the course of CCHF patients have nausea, vomiting, gut bleeding, hematemesis and malena and hence potentially poor uptake of oral Ribavirin. Blood Count needs to be monitored at least weekly. Ribavirin was generally well tolerated. The most common side effect of ribavirin is mild to moderate hemolytic anemia which is reversible. Anemia associated with ribavirin therapy is often asymptomatic and can be managed by monitoring blood count and serum biochemistry. Ribavirin is contraindicated for treatment in pregnant women. Given the high risk of CCHF-related mortality for both pregnant women and fetuses, ribavirin still may be recommended. Ribavirin is contraindicated in patients with chronic anemia and hemoglobin levels below 8 g/dl, and in patients with severe renal impairment (creatinine clearance <30 ml/min). The drug may accumulate in patients with impaired renal function. These patients should be carefully monitored during therapy with ribavirin for signs and

symptoms of toxicity, such as anemia. In case of hypotension and hemodynamic instability patients should be managed on standard guidelines for the treatment of shock which includes resuscitation, fluid supplements (crystalloids/colloids) and inotropic support. In suspected secondary bacterial infection patient should be treated on standard guidelines/practice for community acquired/nosocomial infections. Platelet transfusion may be considered if there is significant bleeding with thrombocytopenia. Ventilatory/renal support may be provided as per the standard guidelines.

Prophylactic administration of oral ribavirin to the contacts of CCHF patients is NOT recommended. Symptomatic contacts can be given therapeutic dose. The complete therapeutic dose of ribavirin should be given to Health Care workers with severe exposure (needle stick injury, direct contact with blood/body fluids). For a person with mild exposure observe and closely monitor HCW for any symptoms. Management of CCHF patients with hyper-immunoglobulin administration might be a very promising new treatment approach, especially for high-risk patients [72].

There are some non-pharmaceutical interventions for patient management that should be followed such as placing patients in an isolation room, prevent non-essential staff and visitors from entering the room, all staff entering the room should wear personal protective equipments, biomedical waste management as per SOP, supervision of infection control practices by hospital infection control committee, the persons handling the dead body in hospitals should wear personal protective equipments, spraying dead bodies with 1:10 liquid bleach and disinfecting ambulance/transport vehicle.

Surveillance of CCHF in India

Currently, there are no standardized case definitions for CCHF notification and contact tracing within India. After the documentation of first positive case of CCHF in Gujarat State a special team was sent to the society where the deceased CCHF positive patient lived and the surveillance on 160 members of the society was conducted for unusual fever symptoms. A similar process was carried out in the case of Shalby hospital by the doctor who had attended one of the CCHF cases. In a special move, the Ahmadabad municipal corporation carried out surveillance in all cattle sheds within corporation limits and abattoirs that operate both legally and illegally. The major concern was the *Hyalomma* ticks that are present on the cattles which are the transmitters of the deadly disease. The strategic actions taken by the State Government included active human, animal and entomological surveillance. Isolation and treatment of cases following universal precautions, contact tracing and monitoring contacts, spraying cattle in the affected area with anti-tick agents, spraying human dwelling with residual sprays and

communicating the risk to the public. In view of the CCHF outbreak, Department of Health, Government of India alerted the states neighboring Gujarat to pick up cases of hemorrhagic fever at the earliest and to review the situation in their states and remain prepared to detect, verify and respond to outbreaks of CCHF. The National Institute of Virology, Pune has been actively involved in surveillance of CCHF in Gujarat and has proposed to carry out nationwide serosurvey of CCHF in domestic animals. Such surveillance will reveal the clear scenario of the existence of CCHFV in different states of India and will help in assessing the possibility of risk by CCHF virus to all the animal handlers in the dairy industry.

Prevention and Control

In the view of the potential consequences during its outbreaks, CCHFV is classified as an agent of bioterrorism. This has resulted in its inclusion as a CDC/NIAD Category-C priority pathogen [73]. After first confirmed CCHF outbreak in India; some important factors have been noticed in hospital settings such as the irregular use of personal protective equipments or barrier nursing methods, minimal use of surgical masks (except in the intensive care units) which might have led to a nosocomial outbreak. Certain universal precautions, such as hand wash was not appropriately followed. Patients did not wear masks in wards or when being transported for medical procedures (e.g., X-ray examination). Disposal of waste, collection of soiled linen, laundry, cleaning of floors and other surfaces in the wards was carried out by personnel who did not follow infection control practices. After the announcement of the CCHF outbreak in India during 2011, stringent infection control practices were introduced, including isolating patients in the hospital, barrier nursing techniques were initiated, and housekeeping procedures and waste management were improved. All these practices and timely diagnosis of suspected cases helped in the management of outbreak and ended with four deaths and one recovery, but again during 2012 similar kind of CCHFV transmission from patient to medical practitioner was reported in hospital settings of Gujarat State [31, 54, NIV unpublished data].

Prevention and control of CCHF infection can be achieved by avoiding or minimizing the exposure to infected ticks. Insect repellents containing N, N-Diethyl-meta-toluamide (DEET) are effective in protecting against ticks. Wearing protective clothing and early and correct removal of ticks are recommended. In endemic areas, control of ticks has been achieved by environmental sanitation of underbrush habitats. Acaricides may be useful for domestic animals to control CCHF virus-infected ticks, if used 10–14 days prior to slaughter or during export of

animals from enzootic regions. Nonspecific preventive measures such as tick eradication has proved to be expensive, inefficient and in many instances impractical.

A vaccine derived from the inactivated mouse brain is used in Bulgaria, but it is not widely available and its efficiency and safety needs to be re-evaluated. Specific human immunoglobulin is used for post-exposure prophylaxis. A DNA vaccine containing the CCHF genome M segment has shown to produce neutralizing antibodies in mice [74]; however, the protective efficacy of the vaccine has not been evaluated.

Recurrence of CCHF in Gujarat State, India

After the nosocomial outbreak in January, 2011, Gujarat State government has taken initiatives to track each CCHF case based on syndromic approach and is undertaking anti-tick measures. However, during June 2012, another episode of nosocomial infections was noticed from Ahmadabad city which resulted in two fatal cases. Exposure history revealed that the treating physician had an accidental contact with the patient (the Index case, resident of Bawla Taluka, Ahmadabad), who had similar symptoms of hemorrhagic fever and had died a week earlier. The sample of the treating physician (Case A) was found to be positive for CCHFV (Unpublished data NIV, Pune). Suspected family contact and hospital contacts and samples of animals and ticks were screened for CCHFV, out of which only animal samples were found to be positive while other contacts and ticks were found negative. During the period of 2010–2012, a large number of referred CCHFV suspected human samples from Gujarat state and other parts of the country were screened by the NIV, Pune but no evidence of positivity recorded from any other state apart from Gujarat.

In the recent years a number of zoonotic viral diseases have emerged in Southeast Asia [75]. CCHF was recently recognized in India; whereas from so many years its presence has been reported from the neighboring countries. The short incubation period and many of the non-specific symptoms overlapping other hemorrhagic fevers, raises the risk of humans carrying the CCHF virus to naive areas. This can lead to secondary infection amongst travel companions, close contacts, and healthcare providers. The environmental factors, climate and human behavior are critical determinants for the establishment and maintenance of CCHF endemicity within an area. Even though the explanations about CCHF emergence or re-emergence have been formulated, the contribution of each of these factors has not been quantified. Those persons who fall in the high risk group populations can reduce the risk of CCHFV transmission through changes in the land use, recreational activities and livestock movement. Increasing awareness about this dreadful disease among people might

help in reducing its incidence rate. Introduction of CCHFV to a non-endemic area could take place either through legal or illegal trade of infected animals, animals infested with infected ticks, through geographic expansion of infected *Hyalomma* ticks from CCHF-endemic areas. The reasons for the emergence and re-emergence of CCHF are multifactorial, which are partly understood. Effective surveillance and reporting of the cases is necessary to monitor the spread of the disease in near future. Multidisciplinary research focusing on developing sensitive diagnostic tools, building biobank of clinical samples, development of new antivirals and vaccines will be useful to prevent or counter/tackle future outbreaks.

Livestock sector plays a critical role in the welfare of India's rural population. Animal husbandry is responsible for a very large economic support to the country and it is estimated that the yearly turnover is in several hundred crores of rupees. It contributes nine percent to Gross Domestic Product and employs eight percent of the labor force. This sector is emerging as an important growth leverage of the Indian economy. India is progressing continuously in the dairy industry. With an annual production of 74 million tonnes in 1998–1999, India is the largest producer of milk [76]. Initiation of Operation Flood in early seventies provided a stimulus to milk production. Gujarat being a hub for the dairy industry, animal exchange, movement and rearing has increased in this State. Hence this disease also raises a crucial concern with respect to the food safety and security point of view in India. In India, Livestock sector in 2010–2011 has contributed Rs. 1645 billion, 3.37 % of total GDP at constant price (GDPLS). According to 18th livestock census in India cattle, buffalo, goat and sheep contributed 199.08, 105.34, 140.54 and 71.56 millions respectively to the economy by various means [77].

Concluding Remarks

The fact that such huge population of the above mentioned livestock is in close contact with the human beings indicates the possibility of spread of this virus in different parts of India. Currently, there is no information available for the presence of this virus in other states. Looking at the scenario a survey is required to understand the prevalence of this disease and risk involved in human health.

As earlier described by Lahariya et al. [32], a national inter-sectoral surveillance and response system, and cross-border sharing of information and establishing special community based laboratory surveillance programs for at-risk population groups should be developed. Laboratory capacity for timely diagnosis with a regional network of accredited laboratories and training of scientific and technical staff, infection control and vector control activities through integrated vector management, biosafety practices

and techniques, case management and health education for high-risk groups and by public health preparedness to address the emerging and re-emerging diseases are the ways to prevent and control this disease.

In a developing country like India only a few Biosafety level-3 laboratories are available, and out of those only a few are capable to carry out viral diagnosis, is one of the main limitations to deal with this infectious disease. Indian council of Medical Research has taken initiative in strengthening virology network and providing bio safety and other training to deal with this situation but this requires multifaceted efforts from all the sectors of public health. Concurrently, it is also very much required to develop a network of health officials at root level to report the cases and co-ordinate with samples sharing, diagnosis and implementation of necessary actions in coordination with state governments for appropriate control of this disease, thus contribute to the benefit and improvement of public health as well as the economy of India at large.

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