Cat Que Virus (CQV): A potential threat of the tropics? "One Health Approach" to avert catastrophe: a narrative review

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Abstract

The world is now experiencing the catastrophe of global pandemic 'COVID-19', most serious public health crises in this century. Recently, another virus named "Cat Que Virus" (CQV) seems to be causing its terrible repercussions in the worlds' largest populous country 'China', the origin of SARS-CoV during 2002-2003, and the current pandemic SARS-CoV-2 since December 2019. Recently, the presence of IgG antibody among two persons in the state of Karnataka for CQV was reported in India, the worlds' second-largest populous country. This means the virus is in circulation in the sub-continent. The presence of the vector mosquitoes (Aedes species, Culex species) and the ambient climatic conditions suitable for vector breeding in the country needs to be taken into account while planning to implement holistic strategies appropriate for control and preventive measures. "One Health approach" is the topmost option covering humans, animals/vectors and the environment to curb the spread/transmission of infectious diseases in general. It is also necessary to study the transmission dynamics and pattern of this emerging virus, its life cycle, the natural reservoir of the virus, the intermediate host and the accidental host with respect South-East Asia, so that necessary remedial action can be planned well before an epidemic. At present, the outbreak of CQV is certainly a warning to the general population around the world. Considering the global imminent health threats posed by CQV, there is an urgent need for active surveillance, monitoring, effective vaccination, and a standard treatment modality of this disease. Given the epidemiological aspect of CQV, control and prevention measures are essential to stop the spread of the virus. At present, there is no information available on CQV; however, this current review article has covered the required data, which will be helpful to control the spread of the CQV.

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Abstract: (293 words)

The world is now experiencing the catastrophe of global pandemic 'COVID-19', most serious public health crises in this century. Recently, another virus named "Cat Que Virus" (CQV) seems to be causing its terrible repercussions in the worlds' largest populous country 'China', the origin of SARS-CoV during 2002-2003, and the current pandemic SARS-CoV-2 since December 2019. Recently, the presence of IgG antibody among two persons in the state of Karnataka for CQV was reported in India, the worlds' second-largest populous country. This means the virus is in circulation in the sub-continent. The presence of the vector mosquitoes (Aedes species, Culex species) and the ambient climatic conditions suitable for vector breeding in the country needs to be taken into account while planning to implement holistic strategies appropriate for control and preventive measures. "One Health approach" is the topmost option covering humans, animals/vectors and the environment to curb the spread/transmission of infectious diseases in general. It is also necessary to study the transmission dynamics and pattern of this emerging virus, its life cycle, the natural reservoir of the virus, the intermediate host and the accidental host with respect South-East Asia, so that necessary remedial action can be planned well before an epidemic. At present, the outbreak of CQV is certainly a warning to the general population around the world. Considering the global imminent health threats posed by CQV, there is an urgent need for active surveillance, monitoring, effective vaccination, and a standard treatment modality of this disease. Given the epidemiological aspect of CQV, control and prevention measures are essential to stop the spread of the virus. At present, there is no information available on CQV; however, this current review article has covered the required data, which will be helpful to control the spread of the CQV.

Keywords: Cat Que Virus; *Orthobunyaviruses*; Vector-borne infection; Tropical nations; Public health; Global threat;

1. Introduction: (1875 words)

The world is now facing one of the most destructive pandemics ever recorded. Panic of death due to Corona Virus Disease-2019 (COVID-19) is all around the world and under the influence of this outbreak, another dangerous virus called Cat Que Virus (CQV) appears to have had its dreadful consequences in China. CQV was first identified from the mosquitoes of Cat Que Commune, Hoai Duc District of Ha Tay Province in Northern Vietnam during the improved surveillance activities for Japanese Encephalitis Virus (JEV), as well as surveys for arbovirus activity in regions where Acute Encephalitis Syndrome (AES) cases had occurred during the period of 2004 causing morbidity and mortality among children due to acute febrile illness and non-JEV AES. Several people in the world have been reported infected so far, and this outbreak is gradually beginning to spread in India as well. The findings of the recent study conducted by the ICMR-National Institute of Virology (NIV), Punereported that 2 out of 883 human serum samples had anti-CQV IgG antibodies. This indicates that these two individuals have been infected by the virus at some point in time. In specific, CQV spreads through pigs and species of mosquitoes known as *Aedes* and *Culex (Ae. aegypti, Cx. quinquefasciatus,* and *Cx. tritaeniorhynchus*). Both of these life forms exist in India and are vulnerable to CQV. CQV can cause diseases such as meningitis, acute febrile illness, and pediatric encephalitis to humans (Shete et al., 2020).

2. Classification of CQV:

The order *Bunyavirales* is found to have more than 350 viruses with tripartite, negative-sense, single-stranded RNA (ssRNA) genomes, belonging to 9 viral families. The members of the *Feraviridae, Phenuiviridae, Fimoviridae, Nairoviridae, Peribunyaviridae, Tospoviridae, Jonviridae* and *Phasmaviridae* families are carried and transmitted through arthropods, while the viruses of the *Hantaviridae* family are carried by rodents and are transmitted through the communication of aerosolized excreta(Elliott, 2013; Whitmer et al., 2018). *Fimoviridae* and *Tospoviridae* family viruses infect plants, while the viruses of family *Nairoviridae*, *Peribunyaviridae* , and *Phenuiviridae* family that contains more than 170 viruses. *Orthobunyavirus* is the largest genus in the *Peribunyaviridae* family that contains more than 170 viruses. *Orthobunyaviruses* are categorized into 49 species and 19 serogroup complexes (Briese et al., 2013; Maes et al., 2018), consisting of extremely diverse arboviruses (Nguyen et al., 2013). Simbu serogroup has been the largest of these with 25 viruses isolated till date (Ladner et al., 2014) and with seven species complexes such as *Akabane, Simbu, Oropouche, Shuni, Sathuperi, Shamonda, andManzanilla* (Zhang et al., 2015; Saeed et al., 2001). CQV is one of the members of the *Manzanilla* species complex belonging to the Simbu serogroup (Figure 1).

3. Symptoms and complications of CQV (Diseases in humans):

In presenttimes, growing numbers of *bunyaviruses* have been recognized as the main human pathogens. Amongst the 170*bunyaviruses*, 60 viruses can induce diseases to humans, containingpediatric encephalitis(*La Cross virus*), fever and joint pain (*Oropouche virus*), meningitis (*Cache valley virus*), Jamestown canyon encephalitis (*Jamestown canyon virus*), febrile illness (*Guaroa virus*), hemorrhagic fever (*Garissa virus*), influenza-like symptoms (*Tahyna virus*) and the recent research were reported that CQV has caused diseases like acute febrile illness (high fever), pediatric encephalitis (inflammation of the brain) and meningitis (inflammation of the meninges) in human beings (Nguyen et al., 2013; Bewick et al., 2016; Treangen et al., 2016; Pastula et al., 2015; Aguilar et al., 2010; Shete et al., 2020).

4. Epidemiology of CQV (Origin and Transmission):

CQV was first isolated in 2004 from mosquitoes and reported during the surveillance of arboviruses in acute pediatric encephalitis cases in Vietnam (Bryant et al., 2005) and late in Uganda (Mossel et al., 2017). Viruses of family *Peribunyaviridae* infect the vertebrates and reside in a zoonotic infection cycle that spreads across livestock and human beings through an arthropod intermediate (Saeed et al., 2001). Globally, arboviruses (arthropod-borne viruses) have turned into a major public health concern with the emergence and re-emergence of arboviral diseases. Most of the arboviruses act as a zoonotic spillover from an infected reservoir hosts (dogs, mosquitoes, birds, and ruminants) to humans (accidental host) (Go et al., 2014; Bodewes and Kuiken, 2018), i.e., the spread of a pathogen from an infected vertebrate to a human is

caused by mosquito bite (Figure-2) (Whitmer et al., 2018).

5. Genome structure of CQV:

Often, the total genome size of *bunyaviruses* ranges from 11 to 19 kb and around 80-120 nm in diameter (Schmaljohn, 1996). *Bunyaviruses* have tripartite genomes containing a large (L), medium (M), and small (S) RNA segments. Among this, the L segment encodesRNA-dependent RNA polymerase(RdRp), which is necessary for mRNA synthesis and replication of the viral RNA. The M segment encodes viral glycoproteins, which ison the viral surface and help the virus in attaching and entering into the host cell. The S segment encodes the nucleocapsidprotein. Both ends of each gene segmentareenclosed with 5'- and 3'-UTRs of various lengths (Ariza et al., 2013; Zhang et al., 2015). Most of the *bunyaviruses*have a negative-sense L and M segment. The S segment of the genus *Phlebovirus* (Elliott and Brennan, 2014) and both M and S segment of the genus *Tospovirus* (Lima et al., 2016) are ambisense. The ambisense M segment codes for glycoprotein (Gc and Gn) in the negative sense and a nonstructural protein (NSm) in the positive sense. The ambisense S segment codes for the viral nucleoprotein (N) in the negative sense and a nonstructural protein (NSs) in the positive sense(Figure 3) (Lima et al., 2016; Bouloy, 1991).

6. Pathobiology of CQV:

The ambisense genome of *bunyaviruses* including the CQV requires two rounds of transcription to be completed. Viral entry into its host cell occurs through the receptor-mediated endocytosis and the following stepstake place in the cytoplasm. Cell receptors are not defined for several *bunyaviruses* (Lozach et al., 2010; Santos et al., 2008; Jin et al., 2002), but those that contribute to the binding of-some *bunyaviruses* contain integrins and other cell receptor proteins, e.g., gC1qR/p32, which is expressed on dendritic cells, platelets, endothelial cells and lymphocytes (Albornoz et al., 2016). As the genome of single-stranded, negative-sense RNA viruses cannot be directly translated, the first step after permeation of the host cell and uncoating in the triggering of the virion RNA polymerase and its transcription and translation, replication of the three virion RNAs. Afterward primary viral mRNA transcription instigates, with favored amplification of the genes that encode structural proteins required for virion synthesis. (https://www.sciencedirect.com/science/article/pii/B9780128009468000222).Virions mature through budding using intracytoplasmic vesicles related to the Golgi complex and are released by the transport of vesicles through the cytoplasm and consequent exocytosis from the plasma membranes (Figure-4) (Weber et al., 2002; https://en.wikipedia.org/wiki/Bunyavirales).

7. Diagnosis:

Most of the diagnostic methods of this virus are carried by the identification of antigen in tissues (immunofluorescence) or serologically by IgG and IgM antibody (ELISA) (Bastos et al., 2012). The IgM capture ELISA method is carried out as a primary diagnostic tool, but reverse transcription-polymerase chain reaction (RTtests are now accessible for identification of the CQV (Zhang et al., 2015; Ladner et al., 2014). Accurate confirmation of the presence of accuratevirus can only bedone through conventional RT-PCRthat is followed by sequencing. However, an earlierstudy has been reported that the CQV has been isolated and then diagnosed by the next-generation sequencing (NGS) method. NGS of agents causing idiopathic human infections have been important in the detection of novel viruses (Whitmer et al., 2018; Yadav et al., 2016). Recently, a precise anda very sensitive multiplexed one-step RT-qPCR were assessed for CQV identification inthe cell supernatants and mouse tissues (Naveca et al., 2017).

8. Prevention by "One Health approach":

One Health (OH) approach has been described by the American Veterinary Medical Association as an integrative effort of multiple disciplines working locally, nationally and globally to gain optimal health for the humans, animals and the environment (American Veterinary Medical Association, 2008). The OH would be useful for a better understanding of the emerging and re-emerging diseases epidemiology, transmission dynamics and pathobiology. Hypothetically, different countries have approached implementing the principles of OH in various infectious diseases with variable success and challenges (Okello et al., 2014). Previously, the Rift Valley Fever (RVF) in Eastern Africa Region during 2006-07 outbreak played a vital role in galvanizing collaboration in OH approaches among researchers, international organizations and government departments to alleviate effects of future outbreaks and catalyzed the essential for perfect understanding and implementation of OH approach with an attention on supporting continued animal health surveillance activities (Breiman et al., 2010). RVF caused by a virus, namely phlebovirus that causesthe disease to animals and mosquitoes and can spread both by animal secretions and mosquito (*Aedes*) bites (Flick and Bouloy, 2005; Linthicum et al., 1998). China has been implementing OH approaches for the coronavirus outbreaks in thepast and the present viz. SARS in 2002-03 and SARS-CoV-2 since 2019 and also for various other infectious diseases as well, which may have been prevented unnoticed (Menachery et al., 2015; Wu et al., 2016; Tan et al., 2017; Zheng et al., 2019; El Zowalaty and Järhult, 2020).Several studies reported that implementing OH approach against COVD-19 (Yoo and Yoo, 2020; Bonilla-Aldana et al., 2020).India also implemented OH surveillance system against COVD-19, which may be helpful tomitigate CQV infection on the whole (Yasobant et al., 2020; Manoj, 2020) to avoid huge loss.

9. Treatment:

As of now, there is nospecifictreatmentmethodfor the infection with CQV. In severe cases, intensive medical care is essential, with the constant monitoring of respiratory activity, control of fluid and electrolyte balance, and the prevention of secondary infections. Ways to prevent the CQV transmission and spread are similar to those routine preventive measures for the spread of other infectious virus estransmitted by mosquitoes (Carpenter et al., 2013; Sakkas et al., 2018). The use of insect repellent, anti-mosquito lotions, wearing a cloth that covers the arms and legs, and proper closing window screens can reduce exposure to mosquito bites, thereby reduging the virus transmission. As an alternative, several natural compounds (picaridin, pyrethrins, and azadirachtin) and plant-derived essential oils (levanter, neem, geraniol, and eucalyptus) have been recommended as mosquito repellents (Carpenter et al., 2013; Hoch et al., 1986). Additionally, source reduction, i.e., removal of stagnant open water sources, including water in flower vases, potted plants, man-made containers, water-circualted air-coolers, referigerators deforst water collection containers, etc., where mosquitoes tend to breed both indoor and outdoors around our house premises, and terrace. Most importantly, follow-general hygiene, limiting contact with vector saliva, urine, feces, or bedding might prevent the spread of the virus (González et al., 2016).

10. Conclusion and Future perspectives:

CQV is zoonotic and originates from pigs and/or mosquitoes. In Vietnam, CQV was first isolated in 2004 and was later discovered in China. Currently, the CQV is impacting and evolving in India and without the proper precautionary measures, it might spread throughout the world. And without proper awareness of this CQV outbreak, we may again be facing a public health crisis or even a pandemic like situation as caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Therefore, to avoid a potential catastrophes in the near future, it is advisable to follow universal preventive measures and precautionary mechanisms. At present, without adequate medicine and vaccination, this is the only way to reduce the incidence of such diseases. In the future, to monitor a potential virus-related epidemic, we must have mandatory criteria for an effective vaccine, treatment modality and medicine. Regarding CQV in particular, there are several aspects that need a OH approach in order to better understand the outbreak and to mitigate further epidemics of a similar public health crisis in the future.

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Figure Legends:

Figure-1: Schematic representation of the Classification of Cat Que Virus (CQV).

Figure-2: Schematic representation of genome of Cat Que Virus (CQV). The genome comprises of Open Reading Frame (ORF) that encoding nucleocapsid proteins (N), external glycoproteins (Gn and Gc), large protein (L), medium protein (M), small protein (S), non-structural proteins (NSs and NSm) and both ends of each gene segment contained 5'-untranslated region (5'-UTR) and 3'-untranslated region (3'-UTR) of different lengths.

Figure-3: Schematic representation of life cycle and transmission of Cat Que Virus (CQV). Birds and/or swine are the primary reservoir hosts of CQV. The virus is transmitted to humans by the infected mosquitoes that have fed from reservoir hosts.

Figure-4: Schematic representation of replication of Cat Que Virus (CQV).

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