



Review Paper

Wetland Viruses and the Increasing Threat of Tick-borne Arboviruses



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ABSTRACT

Arboviruses are responsible for many emerging and reemerging diseases that represent a significant public health threat globally, affecting millions of people annually and putting over half of the global population at risk. These viruses primarily depend on mosquito or tick vectors for transmission to vertebrate hosts. Ticks are one of the major vectors transmitting a wide range of arboviruses that are known to cause serious infectious diseases in both animals and humans. The geographic expansion and increasing prevalence of tick-borne viruses pose significant prevention and control challenges. Amid the global health challenges resulting from the Coronavirus disease pandemic and the recent resurgence of monkeypox, which has been designated a public health emergency of international concern, another febrile illness has been reported in northeastern China that has drawn attention. Recently, a new tick-borne virus, the Wetland virus associated with human febrile illness and closely related to the Crimean–Congo hemorrhagic fever virus, has been identified in a patient admitted to a hospital in Jinzhou, Liaoning Province, China, after a tick bite. The affected individuals showed variable degrees of clinical symptoms. It is essential to remain vigilant about this new viral outbreak. As it is a new virus, there are no reports available demonstrating effective vaccines or drugs for the treatment of the Wetland virus. In this review, an outline of the Wetland virus and insights into the tick-borne arboviral infections are provided. Further, the need for the development of effective treatments, surveillance measures, and prevention strategies to mitigate future outbreaks is also highlighted.

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1. Context

Arboviruses comprise a diverse family of viruses infecting both animals and humans. Most of these viruses pose public health challenges, as they cause severe diseases with substantial mortality and morbidity during epidemics. These viruses circulate among wild animals and are transmitted to susceptible hosts through an insect vector such as infected mosquitoes, flies, and ticks [1, 2]. Ticks are one of the major arthropod vectors for the transmission of human pathogens, including bacteria, viruses, and parasites. The prevalence and distribution of tick populations and tick-borne diseases have gradually expanded due to climate change and human activities and present a threat to global health [3, 4]. The tick-borne viruses are a group of viruses categorized into two orders, nine families, and twelve genera, along with other unclassified members [5], which are carried and transmitted by ticks. Some of these viruses are known to cause severe diseases with high morbidity and mortality rates and are associated with major epidemics. Several tick-borne viruses have been identified so far and have long been a significant concern for veterinary and human health worldwide [6, 7]. Some of the medically important tick-borne viruses are tick-borne encephalitis virus, Crimean–Congo hemorrhagic fever virus, Bourbon virus, Dohi virus, Powassan virus, Omsk hemorrhagic fever virus, Colorado tick fever virus, Heartland virus, and Kyasanur Forest disease virus [8-10]. These viruses are common in many regions and cause millions of infections worldwide. Notably, the high incidence of tick-borne diseases has been reported in China [11]. However, the current knowledge about the association of tick-borne viruses and tick species is limited, and the disease burden is considerably underestimated.

2. Acquisition of data

We conducted a review of relevant articles from Scopus, PubMed, and Google Scholar databases to collect and analyze existing literature on the Wetland virus and the threat of tick borne viruses. The search terms included “wetland virus”, “tick borne virus”, “arboviruses”, “public health impact of tick borne viruses” “ticks control and prevention measures” and the relevant articles were identified. Research papers, review articles, perspectives, and commentaries providing appropriate information that fit with the aim of the study were included. The data from the collected articles were used to highlight the current state of knowledge on the growing public health threat posed by tick-borne viruses.

3. Results

3.1. Wetland virus

Amid the global health challenges resulting from the coronavirus disease (COVID-19) pandemic, the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants [12] and the recent resurgence of mpox [13, 14], which has been designated as a public health emergency of international concern, another febrile illness has been reported in northeastern China that has drawn attention. Recently, Zhang et al., [15] reported a human febrile illness caused by a previously unknown orthonairovirus transmitted by ticks. This vector-borne human illness was caused by a newly discovered orthonairovirus, which was designated as the Wetland virus. The virus was identified in a patient admitted to a hospital in Jinzhou, Liaoning province, after a tick bite at a wetland park in Inner Mongolia, China, in 2019. This virus belongs to the family Nairoviridae under the genus Orthonairovirus. The viral genome consists of a negative sense single-stranded RNA genome segmented into large (L), medium (M), and small (S) segments. The large segment encodes the L protein, which consists of 3948 amino acids, the M segment codes for a glycoprotein precursor with 1436 amino acids, and the S segment encodes the N protein made up of 485 amino acids. This virus is closely related to the tick-borne Hazara orthonairovirus (62.2 to 89.6% similarity), which includes Crimean-Congo hemorrhagic fever virus [16]. The *Haemaphysalis concinna* tick was the possible vector that can transmit the Wetland virus. The female ticks transmit the virus to their offspring through eggs (transovarial transmission) [15].

Wetland virus RNA was identified in five tick species (*H. concinna*, *Haemaphysalis japonica*, *Ixodes persulcatus*, *Dermacentor silvarum*, and *Haemaphysalis longicornis*) as well as in samples from sheep (2.3%), horses (5%), and pigs (0.9%) collected in northeastern China [15]. In a recent study, five other novel Wetland virus tick vectors were identified, including species such as *Ha. qinghaiensis*, *Ha. tibetensis*, *De. nuttalli*, *Hy. asiaticum*, and *Rh. microplus*. The regional prevalence patterns showed vector specialization, with different species dominating in specific regions. Furthermore, various domestic and wildlife animals were found harboring wetland virus-positive feeding ticks, indicating a wide host range for the virus. Serological evidence in animals suggested their role as amplification reservoirs, contributing to the transmission cycle. Wetland virus demonstrated the ability to infect multiple animal hosts, with phylogenetic analysis confirming that ecological overlap drives spillover risk

[17]. However, further detailed investigations are still needed to assess the possible circulation of this virus in ticks, animals, and humans. The pathogenicity of this virus was studied in BALB/c, C57BL/6J, Kunming, and IFNAR1^{-/-}, and C57BL/6J mice by intraperitoneal injection. The virus caused lethal infections, with the death occurring between 2-8 days post infection. In contrast, the virus did not cause mortality in hamsters. High viral loads were observed in the infected mice, while lower viral loads were noted in the hamsters [15].

3.2. Symptoms and treatment

Wetland virus infection in 17 patients in China was diagnosed through reverse transcription-polymerase chain reaction (RT-PCR). The affected individuals displayed non-specific symptoms of Wetland virus infection, including fever (94%), dizziness (65%), headache (53%), malaise (53%), myalgia (29%), arthritis (18%), and back pain (12%). Gastrointestinal symptoms such as nausea, vomiting, and diarrhea were reported in 53% of patients. Neurologic symptoms, petechiae (24%), and localized lymphadenopathy (29%) were also reported in certain cases. As the symptoms are nonspecific, it is necessary to perform a differential diagnosis to distinguish Wetland virus from other tick-borne viruses [15].

As Wetland virus is a newly identified pathogen, there are no reports available demonstrating effective vaccines or drugs for the treatment of Wetland virus. Recently, Wang et al., demonstrated the antiviral activity of ribavirin, remdesivir, molnupiravir, sofosbuvir and 4'-fluorouridine. The results demonstrated that ribavirin and 4'-fluorouridine inhibited virus replication in vitro and reduced mortality in a lethal immunocompetent mouse model. The study concluded that ribavirin and 4'-fluorouridine are promising therapeutic candidates for the treatment of Wetland virus infection [18].

3.3. Control and prevention measures

The risks of tick-borne diseases affecting domestic animals and humans are rising globally. Ticks transmit a wide range of infectious agents to both humans and animals. In addition to the challenges related to the accurate diagnosis and clinical management of tick-borne diseases, the prevention and control of these diseases are often difficult. The prevention and management strategies of tick-borne diseases include minimizing tick exposure or tick bites by avoiding tick habitats and using repellents along with personal protection measures such as wearing protective clothing, such as long-sleeved shirts and long pants, which will reduce the risk of disease trans-

mission [19-21]. Further implementation of vector control measures focusing on chemical, biological, physical, and integrated pest management strategies could reduce tick populations and complement public health-directed educational efforts through social media, campaigns, and advertisements, which could create awareness and promote preventive measures to minimize tick-borne disease risks. Importantly, the development of rapid and specific diagnostic kits/assays and tick-borne virus-targeting antivirals is highly essential to limit the burden of tick-borne diseases on public healthcare systems. The development of efficient, broad-spectrum vaccines that can induce a long-lasting immune response to a wider range of tick-borne viruses could be a valuable contribution to disease prevention globally [11, 22-25].

The recent identification of new viruses, including wetland virus and Langya virus [26], is a reminder that viruses are a constant threat to humans, with more yet to be identified. There are still limited data available about the Wetland virus and much is yet to be learned. The human infection potential of this orthonairovirus is still underexplored. As the initial findings about this virus are based on a limited number of patients in China, this restricts the understanding of the virus's true prevalence and impact. Further research is necessary to determine the severity of this infection, the transmission mechanism, and to assess the extent of spread of the viral infection. Although this newly discovered virus has not cause any major public health concerns so far, it is essential to stay prepared by adopting appropriate preventive measures and implementing proactive control measures that could limit the potential future impact. Additionally, regular screening/testing of vectors and humans is vital for the timely identification of the virus to keep the disease under control [27, 28].

Overall, the public health impact and the seriousness of tick-borne diseases are significantly underestimated. These diseases demand immediate attention from public health experts and the research community. Still, the host and viral determinants of the pathogenesis of many tick-borne diseases are poorly understood [29]. Therefore, it is crucial to strengthen surveillance, vector control, accurate diagnosis and detection efforts, and awareness campaigns to better understand and monitor tick-borne pathogens. This also includes identifying the hosts and vector species that transmit these viruses [30, 31]. This can be achieved by adopting proactive strategies such as implementing comprehensive methodologies for monitoring tick-borne virus distribution, such as real time surveillance, developing portable diagnostic kits for field testing and early detection, establishing a global

database for centralized information, and harmonizing surveillance efforts at the national and international levels. Additionally, the implementation of a one health approach involving various stakeholders from public and private sectors on a global, national, and regional level is particularly relevant for a comprehensive understanding and effective management of human pathogens. This approach requires improved coordination, collaboration, and communication across human, environmental, and animal health sectors by sharing knowledge and resources and identifying gaps in order to effectively address the health threats and improve overall public health outcomes [32-35].

4. Conclusion

The geographic expansion of vectors increases the risk of emerging and reemerging viral infections in previously unreported regions, thereby complicating disease prevention and control efforts. Many viruses that were earlier reported to be existing mainly in rural tropical settings are now distributed worldwide and have emerged as global pathogens. This trend shows the growing concern about the spread of diseases carried by vectors, such as ticks, mosquitoes, and other arthropods, which have facilitated the movement of pathogens worldwide. Tick-borne viruses are a major threat to human and animal health worldwide. In recent times, the number of tick-borne infections is increasing, and it is expected to increase further in the coming years. Timely identification of ticks and the associated pathogens is essential for preventing tick-borne viral diseases. Any disease outbreak should be reported to the health department, which helps to prevent further spread and protect public health. Although the first tick-borne pathogenic virus was identified over ten decades ago, our knowledge about the relationship of tick-borne viruses with their vectors and the disease pathogenesis is still limited. There still remains a gap in understanding the complexity and variability of human disease. Intensive laboratory studies along with the development of suitable in vitro and in vivo models and the application of multiomic system biology approaches are essential in understanding disease pathogenesis and progression of human infections and diagnosis, which help with disease prevention and control measures. A deep understanding of the mechanisms driving factors responsible for disease transmission will help us prevent and control disease outbreaks. The outbreak of diseases in new regions reinforces the call for action against tick-borne infections and the need for improved healthcare infrastructure, trained personnel, and the development of new diagnostic assays, ef-

fective vaccines, therapies, vector control, surveillance measures, and prevention programs for effective disease management.

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Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Data availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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Authors' contributions

Conceptualization, investigation, review, editing, and final approval: all authors; Supervision and writing the original draft: Balamurugan Shanmugaraj.

Conflict of interest

The authors declared no conflict of interest.

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