Editorial

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The pathogenicity and risk evaluation of Rift Valley virus to cause mysterious "Disease X": an update on recent evidences

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Dear Editor,

Disease X is a term coined by the WHO to represent a hypothetical disease that could cause a future pandemic. Therefore, we should emphasize preparedness and highlight the possibility of new or unknown pathogens emerging[1]. The WHO has a list of priority diseases that pose a significant public health risk due to their potential to cause pandemics and the lack of effective countermeasures. The current list includes COVID-19, Cirmean-Congo haemorrhagic fever, Ebola virus disease, Lassa fever, MERS, Nipah and henipaviral disease, RVF, Zika, and Disease X. In 2018, the WHO reported 481 events in 141 countries and territories. This event included both known diseases and new pathogens, referred to as Disease X, which have the potential to cause widespread outbreaks with high fatality rates and no effective preventive treatment or vaccines[2]. Scientists assumed that the next pandemic was more likely to come from a zoonotic disease. Almost all pandemics, Public Health Emergency of International Concern (PHEIC) events, and WHO-priority diseases have been zoonoses, with viruses originating from animals. Scientists are constantly monitoring and studying various organisms to identify the potential causes of disease X. These organisms could be novel pathogens or existing pathogens with novel features. By studying these pathogens, scientists can better understand their characteristics, transmission patterns, and potential to cause widespread illness. They focus on zoonotic diseases because they have been responsible for past outbreaks, so understanding them is crucial[1,3]. The identification of a potential causative organism for disease X is based on several factors. Globalization, urbanization, climate change, and changes in human behaviour can contribute to the emergence and spread of new diseases[1]. It's important to note that Disease X is a hypothetical concept, and scientists are not predicting a specific pathogen.

RVFV is an emerging arboviral pathogen that can cause outbreaks among the vulnerable populations. Kenya reported this mosquito-borne viral zoonosis in 1930. In 2022, there was an outbreak in Mauritania, confirmed by the National Institute of Health Research. Since the 1950s, East and Southern parts of Africa have reported severe RVF outbreaks. In the 1980s, several West African nations experienced an epidemiological shift, possibly linked to climate change. In 2000, the virus was detected outside Africa on the Arabian Peninsula, raising concern about its spread to Asia and Europe through cattle trade. Outbreaks have occurred in several African countries in 2019. The geographic expansion of RVFV highlights its ongoing threat and emphasizes the need for surveillance and control measures to mitigate its impact on public health and economics[4].

The RVF outbreak timing can vary across different regions. In East Africa, a majority of outbreaks (77%) start between November and January. In Southern Africa, about 80% outbreaks begin from March to June. For West Africa, the majority of outbreaks (92%) occur between July and October, while in North Africa, more than half of outbreaks begin between September and October. Even within countries, seasonal rainfall can vary greatly[5]. Climate change is also impacting seasonal weather patterns, making differences in outbreak incidence more pronounced among at-risk locations[6]. However, these changes can make it harder to predict epidemics. It's not just rainfall that increases the likelihood of an outbreak. Factors like the congregation of susceptible hosts, large-scale animal slaughter, an abundance of mosquito breeding sites, extensive animal movement, and low baseline herd immunity all contribute to the chance of RVF outbreaks. During RVF outbreaks, information about the number of cases, prevalence, and factors contributing to infection is often collected from suspected patients rather than comprehensive surveys. Additionally, limited access to affected rural communities, which are often dealing with heavy rainfall and flooding, makes it challenging to conduct outbreak surveys and diagnostic testing. As a result, the transmission and risk factors for RVF-related human disease are not well understood[5].

The RVFV belongs to the phlebovirus family within the phenuiviridae family (previously known as Bunyaviridae). Its genome consists of three segments: large, medium, and small. The small segment contains the nucleoprotein and a non-structural protein (NS). The large segment encodes the viral polymerase, while the medium segment encodes a NS and glycoprotein weighing 78 kDa, along with two structural glycoproteins, Gn and Gc[7]. Multiple studies analyzing the genetic makeup of

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RVFV in Africa and Saudi Arabia found limited genetic variation, with around a 5% difference at the nucleotide level and about 2% at the amino acid level. A comprehensive study spanning 67 years and involving 198 isolates from various countries identified 15 lineages (A-O) based on sequence categorization. The analysis also revealed that different strains can coexist during outbreaks, and there is evidence of genetic reassortment between them[8]. Viral reassortment refers to the exchange of genetic segments between multiple virus strains while infecting the same host cell. However, information about the virulence of different RVFV strains is limited. Specifically, when examining the glycoproteins, researchers observed that the region farthest from the membrane in the Gn protein undergoes the most non-synonymous mutations. Therefore, a particular area of the molecule experiences much more selection pressure and fewer structural constraints[8]. The isolated cases during 2008–2009 were linked to RVFV lineage C, which is widely distributed and has caused outbreaks in Africa and the Arabian Peninsula. The RVFV caused South African epizootics in 2010–2011 by lineage H, which originated in Namibia in 2004. In the Northern Cape province, one isolate belonged to lineage K, which was responsible for a small outbreak in South Africa in 2018[9].

People typically contract RVFV by coming into contact with bodily fluids, such as blood or other fluids, the tissues of infected animals, primarily livestock such as camels, goats, sheep, buffalo, and cattle. This direct contact can occur when individuals come into contact with contaminated objects during animal butchering, taking care of animals, veterinary procedures like assisting with animal birthing, and eating raw or undercooked animal products. Urine or faeces of infected animals can also transmit RVFV[10]. Infection with the RVFV was documented in laboratories during the 1930s–1950s when individuals inhaled the virus present in the air. However, it is currently unknown if RVFV can be transmitted sexually. Vertical transmission occurs from mothers to their unborn babies in human cases, and ex-vivo experiments have shown that RVFV can directly infect human placental tissue. In addition to mosquito bites, people can also contract RVFV through bites from other infected insects, although this is rare. Other arthropods, such as midges, ticks, and sandflies, can become infected with the virus and potentially serve as mechanical vectors[8]. The virus can remain viable in eggs for several years under dry conditions. Increased rainfall leads to more mosquito eggs hatching. Various mosquito species, notably Aedes and Culex mosquitoes, can transmit RVFV, although the specific species can vary by region. RVF outbreaks are often associated with heavy rainfall and flooding, as mosquitoes spread the disease, and increased rainfall facilitates more mosquito egg hatching. There have been no documented cases of RVFV spreading from person to person and no transmission of this virus to healthcare workers[10]. The proper pathogenesis of RVFV is still unknown, antigen-presenting cells in the host are probably the initial target of the virus. Then, it results in suppression of type I IFN production and dermal cell necrosis. After that, it spreads in systemic circulation causing necrosis of other cells of body organs. Lymphocyte apoptosis exacerbates the inability of both the innate and adaptive immune responses to control infection. The impairment of the coagulation system results in haemorrhages. Further, multiorgan failure, oedema in many organs (including the lungs and brain), hypotension, and circulatory shock cause fatal outcomes[11]. Two studies in experimental ex-vivo setting have illustrated that RVFV has the ability to infect placental explants from midgestation and full-term foetuses[12]. Generally, individuals infected with RVFV either experience no symptoms or have a mild illness resembling flu, like fever, muscle and joint pain, and headache[13]. Some patients may develop symptoms such as stiffness in the neck, sensitivity to light, loss of appetite, and vomiting. The RVF symptoms typically last for 4–7 days, and when antibodies become detectable, the virus disappears from the blood[14]. Severe cases, which account for only 2% of all cases, may develop three different complications such as meningoencephalitis ($<1\%$), eye disease (0.5–2%), or haemorrhagic fever $<1\%$). The incubation period for RVFV ranges from 2–6 days. Supportive treatment is often insufficient in more severe instances, and hospitalization is necessary[15]. Healthcare authorities reported the spread of RVFV in 39 countries between 1999 and 2021 based on the detection of acute cases, polymerase chain reaction testing, or serosurvey results. Between 1999 and 2021, 83 reports documented 124 places in 19 countries with 4353 suspected or confirmed human RVF cases and 755 fatalities. Furthermore, authorities reported 107 acute RVF animal incidents among 470 confirmed cases by Office International des Epizooties (OIE in 31 countries[5]. Between 2000 and 2022, the overall prevalence of RVF was 7.8% in humans and 9.3% in animals in Africa[16]. According to the WHO, the case-fatality ratio of RVF is less than 1%, and about 50% of cases are haemorrhagic[15].

Most cases of RVF are mild and resolve spontaneously. Severe RVF patients require hospitalization and treatment. Early, aggressive, and intensive care support can save lives. Close monitoring of fluid balance, kidney function, blood pressure, and oxygen saturation can ensure rehydration. Sometimes, blood component transfusion is required to support the coagulation system. Clinicians recommend anxiolytics for agitation, pain relievers, and anti-emetics for vomiting as supportive drug therapy. However, physicians do not prefer antiviral drugs to manage RVF due to their lack of effectiveness and potential health risks[17].

Currently, there are no approved vaccines for human use. Three licensed veterinary vaccines are available to protect ruminant populations. However, their use in endemic regions is limited. The live attenuated Mo-12 vaccine has conditional licensure in the USA. Authorities have approved the Clone-13 vaccine for use in South Africa and Zimbabwe[18]. To prevent RVF, people can follow health safety guidelines. Avoiding contact with infected, ill, or dead animals, especially livestock such as sheep, goats, cattle, etc., can reduce the risk of contamination. Use gloves and other protective measures when handling animal tissues or fluids. Mosquitoes are the primary vectors of the virus, so it's vital to minimize exposure to mosquito bites. Use insect repellents, wear protective clothing, and ensure windows and doors have screens to keep mosquitoes out. Hygiene practices include regular handwashing with soap and water, especially after handling animals or coming from potentially contaminated surfaces. Ensure proper cooking of meat and other animal products to kill any potential pathogens. Avoid consuming raw or undercooked meat[14,17].

It is essential to control animal movements and take precautions at slaughterhouses to prevent the spread of the disease from animals. However, efforts to control vectors and maintain sanitation may be less effective during the ongoing outbreaks. Active surveillance is crucial for detecting new cases of RVF and issuing early alerts to veterinary and public health authorities[4].

RVFV is a major emerging arboviral pathogen that has spread in several regions. It has significant health impacts on vulnerable populations. It is considered a priority pathogen by WH0, FAO, and CDC due to its potential to cause life-threatening diseases in humans and livestock, and it can spread rapidly during outbreaks. The severity of human RVF is associated with concurrent co-infections. In a travel-related case, a fatal outcome may occur in the presence of concurrent hepatitis. A study conducted during the 2010 RVFV outbreak in South Africa found that individuals with existing HIV-positive status were at risk for the encephalitis form of RVF disease. Tanzania experienced similar cases of RVF with HIV infection in 2007, where all HIV-positive patients developed encephalitis, and the mortality rate was 75%. In Kenya, handling sick animals and consuming their products were strongly associated with severe human RVF. Heavy rainfall and mosquitoes drive livestock infections, while human outbreaks can be influenced by slaughtering sick animals and secondary mosquito vectors. Livestock viral amplification plays a crucial role in the occurrence of human cases[5]. In 2000, RVFV was detected outside of Africa on the Arabian Peninsula, raising concerns about its potential spread to other regions in Asia and Europe[4]. Our knowledge about its spread, development, and immunity is limited, although scientists identified RVFV in the 1930s[19]. If the virus were to emerge in non-endemic areas, the lack of human vaccine, direct contact or aerosol transmission, and the severity of the disease could challenge the health of both humans and domestic animals[18]. We can manage various emerging, re-emerging, and stable vector-borne diseases effectively nowadays. However, efforts to prevent the emergence of new diseases remain uncertain, highlighting the need for a continuous fight against emerging vector-borne infections[20–22].

RVF is a persistent threat to livestock and animals, requiring our attention and proactive measures. In conclusion, it is crucial to prioritize research and development efforts to create licensed human vaccines and therapeutics, as this would enhance our ability to control and prevent future outbreaks. The WHO recognizes the urgency of this matter and has highlighted the need for immediate action. Collaboration between governments, researchers, and healthcare organizations is essential for effectively combating RVF. Additionally, raising awareness among communities about the disease, its transmission, and preventive measures can play a vital role in minimizing the impact of future outbreaks. By investing in research, strengthening surveillance systems, and promoting public education, we can work towards mitigating the risks associated with RVF and safeguarding both human and animal health.

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