Entomology and Applied Science Letters
Volume 7, Issue 1, Page No: 68-75

Available Online at: www.easletters.com

ISSN No: 2349-2864

Neglected Tropical Disease of Rift Valley Fever and Its Impact on Human, and Animal Health with Emphasis on Iran: A Review Article

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ABSTRACT

Introduction and Objectives: Rift Valley Fever (RVF) is an acute viral hemorrhagic zoonotic disease that is transmitted to humans through mosquito bites or contact with infected livestock. The primary RVF vectors are *Aedes* species. Other mosquitoes such as *Culex*, *Anopheles* and *Mansonia* are considered secondary vectors. RVF is important from a public health and economic perspectives. Africa and the Middle East have been identified as a primary foci for RVF. Neighboring Iran, Saudi Arabia is one of the endemic foci for the RVF. According to a recent report pointing to RVF incidents observed among ruminants in Kurdistan Province, Iran, this study was conducted to evaluate the status of this disease and its possible occurrence in Iran. **Materials and Methods:** In this study, the websites of reputable medicine and health journals, as well as scientific databases were searched to find relevant articles using many keywords. Out of 111 articles, finally, 77 cases were selected and analyzed according to the aim of the study or RVF status in Iran. **Results:** In 2016, the first RVF positive serological report in animals in Iran was carried out in Kurdistan Province, indicating the risk of animal exposure to the virus. According to the observation of RVF cases in animals, the risk of human RVF cases in Iran has also increased. Annual travels of people to neighboring countries increase the probability of the RVF virus entering to Iranian society. **Conclusions:** Given the geographical location and proximity to the foci of primary disease, the risk of RVF endemicity in Iran is extremely high. Every year, a large number of people travel back and forth between Saudi Arabia (an active disease hotspot) and Iran, and large quantities of meat and livestock are exported from Saudi Arabia to Iran. In light of the specified issues and positive serological report of RVF in cattle and sheep in Iran, the necessity of careful supervision, planning, and monitoring to prevent the entry of human cases to the country or spreading the disease becomes apparent.

Keywords: *Epidemiology, Rift Valley Fever, Arbovirus, Vectors, Reservoirs, Control, Surveillance, Iran.*

HOW TO CITE THIS ARTICLE: Hamid Kassiri, Rouhullah Dehghani, Maral Kasiri, Mousa Dehghani ; Neglected Tropical Disease of Rift Valley Fever and Its Impact on Human, and Animal Health with Emphasis on Iran: A Review Article, Entomol Appl Sci Lett, 2020, 7 (1): 68-75.

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Received: 09/09/2019
Accepted: 27/02/2020

INTRODUCTION

Rift Valley Fever (RVF) is an acute mosquito-borne viral disease that mainly affects ruminants, with the potential to also infect humans. This can cause miscarriage in pregnant animals. High miscarriage and neonatal mortality rates are most commonly seen in sheep, goats, and cattle afflicted with the disease. In humans, the virus causes a disease similar to severe influenza and may occasionally cause complications such as excessive bleeding and death. The major

outbreaks of this disease are seen at irregular intervals of 5–35 years [1–3]. The RVF virus belongs to the family Bunyaviridae of the genus *Phlebovirus*. RVF virus is a single-stranded RNA virus that has only one serotype, but strain differences in virulence. It primarily affects livestock and causes epizootic in a large number of domestic animals such as sheep, cattle, goats, and camels. The disease then affects people who come in contact with infected animals [4-7]. Heavy rainfalls are often reported before outbreaks. Mortality rates vary across epidemics but are generally less than 1%. However, post-infection complications are very high in number and can have a serious impact on the economic situation. Most human cases are relatively mild. Many patients experience severe symptoms such as influenza, including sudden onset of chills, muscle pain, back pain, headaches, nausea and fever that persist for a week or more. However, in a small number of patients, a much more serious form of the disease is present. These include ocular, meningoencephalitis and bleeding syndromes. The majority of deaths occur in patients with the bleeding syndrome (especially internal bleeding) [8-10].

Human RVF infection is caused by direct or indirect contact with the blood, tissues, or organs of infected animals, especially during butchery or slaughter. The virus enters the body through knife wounds or skin scratches. As a result, butchers, shepherds, slaughterhouse workers, veterinarians and those involved in the preparation of meat products are more susceptible to infection [11, 12]. However, mosquito bites represent the main mode of transmission. The disease may be transmitted through sandflies bites belonging to the family Psychodidae, such as *Phlebotomus duboscqi*, *Phlebotomus papatasi*, *Phlebotomus sergenti*, and *Sergentomyia schwetzi* [13-16]. *Aedes* mosquitoes are the primary vectors of the disease and mosquitoes such as *Culex*, *Anopheles* and *Mansonia* are considered as secondary vectors. The virus is transmitted vertically to *Aedes*' eggs [17]. The disease can also be transmitted mechanically through bloodsucking flies (*Stomoxys*, tabanids, and midges) [18].

Endemic foci of the disease are in Africa and Saudi Arabia, with numerous cases being reported each year [19, 20]. Given the importance of this disease, studies have been conducted on the presence of RFV in Iran. Following the outbreak of RVF in Saudi Arabia in 2000, human and animal surveillance in Iran has increased until 2011. From 2001 to 2011, 1206 sheep, 405 goats, 325 cows, and 28 camels were tested for RVFV in 9 provinces of Iran. None of the tested samples were IgG positive. None of the 37 clinically suspected human cases with RVF symptoms were RVFV positive [21]. In 2016, however, the first animal case of RVF (with serological evidence) was reported in Kurdistan province (western Iran). In this study, 288 ruminants (cattle, sheep, and goats) were tested for the presence of specific RVFV antibodies using ELIZA and IIFA methods. Five animals (1.74%) including two cows (1.7%) and three sheep (2.11%) were finally identified as being IgG positive. All animals were clinically normal [22]. According to current data, the importance of RVF in Iran is increasing.

The Rift valley fever has currently become endemic in countries neighboring Iran, including Saudi Arabia. On the other hand, cases reported in Iran have confirmed animal infection. Each year, tens of thousands of Iranians travel to Saudi Arabia to attend the Hajj pilgrimage, which may cause some Iranian pilgrims to become infected with the RVF virus. Therefore, RVF can cause some health problems as an emerging disease in Iran. According to this description, it is very important to study the status of this disease and its effective preventive measures. The present study was conducted for this purpose.

MATERIALS AND METHODS:

The ethical principles of this study were investigated and discussed in the Medical Entomology Department, School of Health, Ahvaz Jundishapur University of Medical Sciences and approved after necessary modifications. This study has been done in accordance with the provisions of the Hillsinki Declaration. Ethical issues are completely observed by the authors. All named authors meet with the International Committee of Medical Journal Editors (ICMJE) criteria to the author of this manuscript, take responsibility for the integrity of the work as a whole, and provide final approval for publication of this manuscript. The datasets analyzed during this study is available from the corresponding author on reasonable request.

In this study, the websites of reputable journals of medicine and health, as well as scientific databases such as Web of Science, Ovid PubMed, SID, Iran Medex, Scirus, Google Schoolar, and Medline, were searched to find relevant articles conducted between 1931 to 2019 using many keywords such as Rift Valley Fever (RVF), distribution, hemorrhagic fever, symptoms, epidemiology, transmission methods, clinical manifestations, treatment, prevention, reservoir, vector, and control. Out of 111 articles, finally, 77 were selected and analyzed according to the aim of the study or the RVF status in Iran.

RESULTS AND DISCUSSION:

Wet seasons and floods prepare the ground for hatching the eggs of the primary vectors, namely several species of *Aedes* that feed on indigenous mammals. High levels of viremia in these animals infect secondary vectors, resulting in infection of other mammals and livestock. In addition, the virus causes miscarriage and death in susceptible animals [23].

The first human RVFV infection was reported after it was isolated in 1930. Until 1951, there was no major human outbreak of the disease when approximately 20000 human cases were reported in an epizootic in livestock (sheep and cattle) in South Africa [24].

Transmission of RVF from animal to human is realized through RVFV vectors, blood aerosols, amniotic fluid or direct contact with infected animal tissues, blood, secretions, and excretions. RVF plays an important role in military purposes and bioterrorism. There is evidence that humans are infected by drinking raw (unpasteurized) milk. Human-to-human transmission of the disease has not been reported so far [20, 25, 26]. In humans, RVF has a wide variety of clinical manifestations, from symptom-free infections or benign febrile illnesses (with flu-like symptoms including fever, headache, lethargy, photophobia, nausea, and muscular pain) that will recover within 4-7 days to acute forms of the disease, observed in approximately 1-3% of cases, which can cause hepatitis, retinitis, haemorrhagic fever, encephalitis, petechiae, blindness, and death. The incubation period is 1-6 days in humans and 12-36 days in lambs [27].

The first outbreak of the disease occurred in sheep in a region in the Great Rift Valley, Kenya, in 1930; for this occasion, this disease was called Rift Valley fever. Serological evidence of infection in humans or animals has also been found in many African countries. The most important reports of the RVF epidemic in livestock were associated with Kenya in 1950 and 1951, killing one hundred thousand sheep. From 1975–1993, several episodes of RVF outbreak were reported in West Africa, Madagascar, Egypt and particularly Kenya [28–31]. Serological evidence has subsequently shown that RVF has spread from Africa to the Middle East [32]. In 2000 and 2001, the prevalence of haemorrhagic fever was reported in humans in Saudi Arabia -Yemeni border area, which was associated with mortality in animals of the same region. Symptoms include fever, abdominal pain, vomiting, diarrhea, jaundice with renal and liver dysfunction and death. RVF was subsequently confirmed in patients by ELIZA and PCR tests. This was the first RVF case approved outside Africa [33]. Out of 886 RVF cases reported in Saudi Arabia between 2000 and 2001, 51.1% were RVF IgM-positive, 35.7% were RVF antigen-positive and 13.2% were both IgM- and antigen-positive. Routine livestock vaccination in Africa is very expensive and has resulted in RVF survival in most African countries. The risk of RVF entry into the United States and Europe is low, but the risk of sporadic entry of RVF is likely to be high [24-26, 34]. The first RVF-induced death in humans was recorded in South Africa in 1977 before which RVF was limited to sub-Saharan Africa. The RVF spread to Kenya from 1997 to 1998 and caused the death of 170 people. The RVF defeated Sudan in 1976 [23, 35]. Found in 1977, in new geographical areas as well as in Egypt. The RVF epidemic in East Africa between 1997 and 1998 caused 89000 infections and 200 deaths. It was the largest epidemic in East Africa, with many reports indicating up to 300 deaths [36- 38].

Currently, Middle Eastern countries, including Iran, are most at risk for developing RVF. This is due to irrigation networks consisting of canals for agricultural purposes that create conditions for widespread mosquito breeding. Iran has good climatic conditions that facilitate the spread of vectors throughout the country [39]. On the other hand, Iran is located close to Saudi Arabia, which increases the risk of RVF entry, outbreak, and endemicity. Among the viruses transmitted by arthropods, RVF is one of the

diseases that can be transmitted by numerous arthropods, but mosquitoes such as *Aedes* and *Culex* play the most prominent role in this regard. Worldwide, more than 30 mosquito species of seven genera, including *Aedes*, *Anopheles*, *Coquillettidia*, *Culex*, *Eretmapoites*, *Mansonia*, *Ochlerotatus* are capable of transmitting RVF [30, 40-43]. Apart from mosquitoes, RVF has been isolated from arthropods and other insects such as sandflies, stable flies, *Culicoides*, *Simulium*, as well as ticks of *Amblyomma* and *Rhipicephalus* [44-47]. However, the virus transmission capacity may vary in different regions for the same vector species. Therefore, the vector capacity of each vector must be examined in each region. Factors such as season, host density, and host preference of vectors can influence RVF virus transmission efficiency [48, 49].

As a country in Asia, Iran has a variety of mosquitoes and potential RVF vectors. Therefore, if human cases of RVF enter the country, it can endanger health [50-54]. Sixty-nine species of mosquitoes belonging to the family Culicidae have been reported in Iran, of which 31, 19 and 12 belong to the genera *Anopheles*, *Culex,* and *Aedes*, respectively, and the rest to other genera. Mosquitoes belonging to the family Culicidae are the most important domestic and public health pests in Iran. These mosquitoes have spread throughout the country. Studies show that mosquitoes of this family are highly abundant in all provinces of Iran and, are capable of transmitting various diseases to humans and animals in addition to pestering, biting, and blood-feeding [55-61].

RVF is associated with the economic and sociocultural status of societies. Therefore, recognition of these factors and promoting public health and awareness is essential to prevent this disease [62, 63]. Most RVF cases in humans are relatively mild and require no special treatment. However, in severe cases, the main treatment is support provision. The inactivated vaccine is currently being developed for humans [64, 65]. People in contact with animals or infected people are at risk for the development of RVF. There is a risk of transmission of the virus through the blood and tissues of infected animals, as well as laboratory and medical equipment. Comprehensive precautions should be exercised by healthcare personnel, especially those in contact with laboratory specimens and secretions of the patient's body. They should wear appropriate and protective gloves and clothing when in contact with infected animals or people, and use special protective methods during hospitalization of patients and transporting specimens of suspected patients [66, 67]. In animal RVF epidemics, the following actions should be taken: monitoring slaughterhouses, vaccinating workers, treating animals until complete recovery or killing infected animals, vaccination of animals, vectors control, restricting the movement of wild and domestic animals from infected areas, observing precautions when contacting infected animals, collecting as well as transporting, and examination of specimens from infected animals, and vaccination of high-risk individuals in deserts or laboratories [68-72]. It is vital to prevent mosquito bites by wearing clothing that covers the body as much as possible (such as long pants and long-sleeved shirts), using insecticide-treated bed nets, using repellents for non-covered areas of the body, use of larvicides in the breeding sites as well as removing larval habitats. Runoff water from seasonal and monsoon rainfall should be directed, as it is usually associated with reproduction and increase of the vector population [73-75]. Utilizing weather forecasts and satellite data and images in early warning systems can be an effective step in monitoring and preventing disease and reducing subsequent consequences [76, 77].

CONCLUSIONS:

RVF is mostly reported in Africa. In 2000, the first confirmed outbreak of RVF outside Africa was reported in two neighboring countries of Iran: Saudi Arabia and Yemen. Therefore, the risk of RVF entry into Iran is extremely high, due to its geographical location and proximity to major disease foci. On the other hand, a large number of people travel back and forth between Saudi Arabia (an active disease hotspot) and Iran every year, and large quantities of meat and livestock are exported from Saudi Arabia to Iran, necessitating careful supervision, planning, and monitoring to prevent the entry of human cases to the country or the distribution of disease. The monitoring of RVFV in susceptible animal species is required regularly. The basic principles of preventing the entry and spread of arboviral diseases include environmental sanitation and

water flow due to seasonal and monsoon rainfall, as they are usually accompanied by the proliferation and growth of vector populations. It is essential to include relevant courses in the student curriculum as well as to increase public awareness of RVF transfer methods using mass media and health planners at the macro level.

ACKNOWLEDGMENTS:

The authors would like to express their gratitude to the Deputy of Research, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran and the Deputy of Research, Social Determinants of Health Research Center, Kashan University of Medical Sciences, Kashan, Iran for their cooperation.

Conflicts of interest:
The authors report no conflict of interest.

Financial disclosure:
There were no sources of extra-institutional commercial findings.

Funding/Support:
No funding.

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