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Review Article: The role of mosquitoes in transmitting some pathogens

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Abstract: Mosquitoes are one of the most important vectors of diseases for humans and animals caused by bacteria, parasites and viruses, including malaria, dengue fever, Zika and RVF. Rift Valley Fever (RVF) is a zoonotic viral disease transmitted by various species of mosquito that infects animals and human alike. The disease is transmitted from the infected animals or through contact with their blood or tissues. The virus remains inside the drought-tolerant eggs in moist or semi-dry soil for many years. It is a disease without symptoms at first, yet it causes economic and health losses to animals and humans. Since there is no available vaccine for the animals and the absence of a licensed vaccine for humans, it is considered an epidemic disease. Its distribution extends from Africa to the Kingdom of Saudi Arabia and Yemen, and for fear of the disease spreading to other regions of Asia, efforts must be made to uncover risk factors and insect habitats to get health prevention and mosquito control.

Key words: Rift Valley Fever, Virus, mosquito, vaccine, epidemic.

1. INTRODUCTION

Arthropods especially insects are considered as important pathogens-carrying that infect human and animal and cause a variety group of severe diseases in all of the world as it is explained in table (1) . It was found that more than 17% of epidemic diseases represent the diseases which are transported by vectors and may resulted from parasites or bacteria or viruses. There is a growing worry associated with diseases transmitted by vectors , as it cause more than 700000 death case yearly because of globally geographic dispersion of many insect vectors , climatic changes and wide trading (WHO , 2002;Caminade et al., 2014) .

Mosquito is an important vector of pathogens , it transmit a large group of diseases which cause around 500000 death case yearly , and there is a danger from exposing to diseases transmitted by mosquito for more than half world population , it was reported every year more than one billion case of these diseases , one of these diseases is malaria , it is parasitic disease caused by Plasmodium parasites and transmitted by *Anopheles* sp. mosquito , it causes up to 219 million infection case in the world and more than 400000 death case yearly (Tolle , 2009 , WHO,2014 , 2020) . As mosquito transmit nematode parasites or filarial parasites which are *Wuchereria bancrofti* , *Brugia malayi* and *B. timori* that cause human lymphatic filariasis disease , around 120 million person were infected by these parasites which cause distortion and swell for hands , legs and sexual organs (WHO,2002 , 2013) .

As mosquito transmit many of viral diseases like Japanese Encephalitis (JE) , which is transmitted by *culex* sp. and the pathogen is virus that belongs to flavivirus known as JEV , the hosts of this virus are birds and pigs and it disperses in south and east of Asia (Rosen ,

1986 , Calisher and Waltson , 1996) . Also *culex* sp. transmits west nile virus (WNV) that spreads in Africa , USA , Europa and west Asia (Troupin and Colpitts , 2016) .

Dangue fever is one of the other viral diseases that transmitted by mosquito , Bhatt et. al. (2013) referred that infection by dangue virus was determined as around 96 million case yearly . Chikungunya fever is another viral disease that mainly transmitted by *Aedes aegypti* and *A. albopictus* , it is an important disease in Africa and south east Asia (De Lamballerei Xde et. al.2008 , Bonilauri et. al. 2008) . Yellow fever disease spread in all tropical and subtropical regions of the world and it is considered a native in Africa and South America , it is transmitted by *A. aegypti* and although there was a vaccine used against it since 1936 , nevertheless it was found nearly 51000-380000 infection case yearly and may the number of lethal cases reach to 18000 in Africa (Barrett and Higgs, 2007 , Garske et. al. 2014) . *A. aegypti* and *A. albopictus* are considered the main vectors of Zika virus which belongs to Flavivirus genus , it resulted in more than 223000 infection case in America until 2017 (WHO , 2017) .

Rift valley fever disease spreads in many of African countries , it infects human and pets , the virus pathogen that causes this disease belongs to bunyaviridae family and phlebovirus genus . This disease identified for the first time in Kenya during the year 1931 (Daubney et. al. 1931 , Peters and Linthicum , 1994) . It will be widely touched upon mosquito role in transmitting Rift valley fever .

What is Rift Valley Fever ?

Rift Valley Fever (RVF) is an epidemic zoonotic disease. It is one of the most serious viral diseases common to humans and animals. It affects mainly human and livestock (cattle , buffaloes , sheep, camels, etc.) (Tantely al et, 2015). The disease is transmitted biologically by mosquito bites. There are more than 30 species of mosquito belonging to 12 genera , including, *Culex*, *Anophelis*, and *Aedes* that have a role in transmitting the infection from livestock to human .

Table (1) a non-exhaustive list of vector-borne diseases (from WHO,2020)

Vector		**Disease**	**Type of pathogen**
Mosquito	*Aedes*	Chikungunya	Virus
		Dengue	Virus
		Lymphatic filariasis	Parasite
		Rift Valley fever	Virus
		Yellow Fever	Virus
		Zika	Virus
	Anopheles	Lymphatic filariasis	Parasite
		Malaria	Parasite
	Culex	Japanese encephalitis	Virus
		Lymphatic filariasis	Parasite
		West Nile fever	Virus
Aquatic snails		Schistosomiasis (bilharziasis)	Parasite
Blackflies		Onchocerciasis (river blindness)	Parasite

Fleas	Plague (transmitted from rats to humans) Tungiasis	Bacteria Ectoparasite
Lice	Typhus Louse-borne relapsing fever	Bacteria Bacteria
Sandflies	Leishmaniasis Sandfly fever (phlebotomus fever)	Parasite Virus
Ticks	Crimean-Congo haemorrhagic fever Lyme disease Relapsing fever (borreliosis) Rickettsial diseases (eg: spotted fever and Q fever) Tick-borne encephalitis Tularaemia	Virus Bacteria Bacteria Bacteria Virus Bacteria
Triatome bugs	Chagas disease (American trypanosomiasis)	Parasite
Tsetse flies	Sleeping sickness (African trypanosomiasis)	Parasite

It is one of the periodic diseases which rain falling for a long time or the excess of irrigation and irregular water administration provide favorable conditions for reproduction of the infection vectors that causes an epidemic cycle (Hoogstraal et. al. 1979 , Swanepoel and Coetzer, 2005). Inflammation occurs as a result of this disease without any appearance of any symptoms . There is a recognized risk of global spread as the World Organization for Animal Health has put this disease at the priority of the WHO for research and development due to its potential to cause major epidemics for human (Peters and Linthicum , 1994) that appeared in some countries of Africa and Arabian peninsula (Davies, 1975). The seriousness of the disease lays in its quickly spread and to its symptoms that resemble the regular flu symptoms and in the lack of awareness regarding health guidelines and measures among workers in pastures and slaughterhouses during their dealing with infected animals or their fluids and blood. It also spreads through importing wild, domestic ruminants and experimental animals , such as white mice and hamsters , where the virus transfers silently among these animals and the insect vectors . This hidden transmission of the disease is difficult to detect (Geeing and Davies, 2002). The recent outbreak of the disease in Madagascar may have been due to importing domestic animals from east Africa (Andriandimby et al, 2010). Previously, the impact of RVF on international trade increased after its spread in human societies was discovered that it due to the absence of clear symptoms on animals, and therefore it is difficult to distinguish infected animals and the control of the disease only takeplace after heavy economic losses occur (Antoine-Moussiaux et al, 2012) .

Causative Agent

The virus that causes (RVF) belongs to the Phlebovirus which is one of the five genera belong to the order Bunyaviridae . The virus was identified, for the first time, in 1931 during the investigation for the epizootics that occurred among sheep on a Rift Valley farm in Kenya. Since then, cases have been reported in the countries of sub-Saharan and North Africa (Tantely et al, 2015). In the years: 1997 and 1998, a pandemic case occurred in Kenya, Somalia, and Tanzania, revealing the viruses in the isolates taken from mosquito , human

and livestock (Clerc et al, 1979; Ratovonjato et al, 2010). In September 2000, many cases of RVF were confirmed in the Arabian Peninsula where the geographic pandemic spot extended to involve Saudi Arabia and Yemen for the first time of the disease occurrence outside the African continent (Madani et al, 2003) that raised concerns about the possibility of disease spreading to other regions in Asia and Europe (WHO, 2017) .

Virus properties

The virus is characterized by its survival in the environment for a long time as it can remain alive for 77 hours in the dry secretions of the animals' stomach and aerosols at a temperature of 25˚ C and relative humidity of 3% (World Organization for Animal Health ,2013 ; Moutailler et al. 2008) . The virus can survive in serum for three years at -4 C and in blood at 0 to 4C and pH 8. The virus is one of the types covered with an outer lipid-protein sheath , so it is inhibited by exposure to fatty solvents and other types of acute solutions and disinfectants, including sodium and calcium hypochlorite . The virus is killed at low ionization degrees, less than 6.2 This case applies to meat since the virus is destroyed when the animal is slaughtered, turning the medium into an acidic pH(Vaburay et. al. 2013) .

Mosquito's role in virus transmission in the nature

The subject of RVF has been of scientific interest for some time , as we know that it remains endemic in case not known then epidemic occurs. There is specific and significant evidence that the virus is transmitted by ovaries in mosquito (Transovarial transmission). Genus *Aedes* is responsible for the cycle of habitation and primary infection to the mammalian hosts . These genera are reproduced in regions of flooding . They appear in huge numbers in the flood plains , where the females lay their eggs . The eggs and the viruses that carried remain alive for a long time in the dried clay during drought period on the surface of ponds or shallow depressions. When the flooding comes again, the mosquito's eggs carrying viruses hatch which show how the virus sustains during long periods between epidemics in pastures and semi-arid areas (Linthicum et al, 1985; Anyanba et al, 2010). The genus Aedes, is suspected to be a contributing factor to the outbreak of the disease in Niger. The presence of this genus species are not sufficient to cause an outbreak of the disease, as it arent an effective species for transmitting this disease between mammalian hosts . Otherwise, species belong to the genus *Culex* are secondary vectors between mammalian families . They are efficient and responsible for increasing the clinical acuteness of the disease and transmitting it from infected animals to a human or another healthy animals . Small outbreaks of RVF may occur locally when and where the environmental favorable conditions are found, with animal herds susceptible to infection besides the presence of insect vectors where the disease incidence is low and the clinical symptoms are usually absent even with the absence of the active prevention (Murithi et al, 2011).

Mechanism of the disease transmission to human

The infection is transmitted to human by the mosquitoes carrying virus (biological transmission) . The mosquito absorbs human or animal blood at the fever phase where the virus exists in it (viremia) that becomes contagious after a period of 21- 28 h. The virus transfers to the ovary, and then the resulting eggs are carriers of the virus (Tantely et al, 2015). Furthermore, the disease is transmitted by the direct contact with the blood, fluids, or tissues of the slaughtered infected animals as well as through inhalation of aerosols from the tissues of infected animals or their fetuses during veterinary procedures, including assisting in the birth or wounding the skin with a contaminated knife . The infection may also occur through touching the skin of a wounded person or has cracks or sores in the skin to blood ,

organs , or secretions of animals (Mohamed et al, 2010) . The virus infection can also occur in the laboratory (acquired infection) during dealing with the virus itself or contaminated tools, so the recommended personal protective equipment should be used (CDC, 2009). There is some evidence related to the possibility of getting an infection as a result of drinking milk from infected, unpasteurized, or unbilled animals; or by blood-sucking flies.

Disease outbreak period

The virus spread across sub-Saharan Africa . Until recently , the existence of RVF was limited to Africa . However , it was reported in the Tuhama region , west of Saudi Arabia and Yemen in September 2000 , where 118 human deaths appeared and 855 cases of abortion in animals . The virus was similar to that spread in Kenia and Somalia in 1997-1998 when a large-scale outbreak occurred in southern Africa between 2008-2011(WHO , 2013) . Figure (1) illustrates that the virus increases with each successive outbreak, regardless of the environmental conditions such as rainfall and temperature, in addition to the density and movement of livestock as well as the presence of vectors represented by different types of mosquitoes (Linthicum et al. 1985; Chevaller et al. 2004). The disease also spread in Madagascar in 2002-2010 (Linthicum et al. 2016). Infection cases were documented in camels in Morocco (El-Harrak et al, 2011). Infection cases were reported in Niger in 2016 (WHO, 2016). Figure 1 demonstrates a study conducted in Mando in 1979 investigating the spread and outbreak of the virus. It is noticeable an increment in the studies about wild animals during the years 2006-2008 (Clark et al. 2018) .

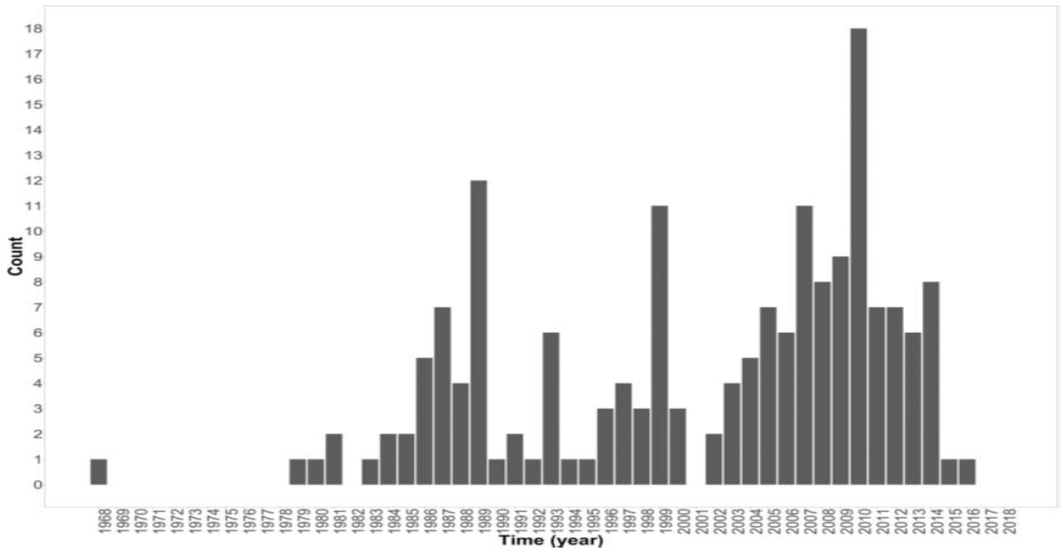

Fig 1. Number of Rift Valley fever virus (RVFV) seroprevalence studies conducted in African countries

Hydrology role and the danger of disease spread in Iraq

Outbreak cases of RVFV infection occur in societies that suffer from climatic changes such as contineous rains. It rarely occur in conjunction with dam construction and irrigation programs, as in Senegal and Egypt. Studies in the coastal areas of West Africa refer to that the outbreak cases are not necessarily correlated with heavy rainfall ; however, the rainfall pattern is a limited and important factor. Even in the years with normal levels of precipitation , long periods of rain with a short dry period are preferable to a dual cycle of local vectors of mosquito's genus *Aedes* and genus *Culex* , which also contribute in resulting a waves of these

vectors simultaneously (Soti et. al. , 2012; Caminade et al, 2014). With climate changing , the frequency and intensity of extreme weather events are expected to increase, including Nino (the periodic changes in sea surface temperature and associated winds in the eastern Pacific Ocean) that form weather in the tropics and subtropics (Patz et al, 2005; Cai et al 2014; Lwande et al 2015) which is expected to change the spatial distribution of the disease, with significant impacts on human mortality rates (Patz et al, 2005). The expected development of the environmental conditions and the insects vector density leading to the spread of RVF disease will change the disease population patterns involving the high-risk future area including the delta of Tigris and Euphrates rivers in Iraq and the Islamic Republic of Iran .

Disease symptom in human

The disease may not be accompanied by any symptoms as the infection is mild, and sometimes the symptoms appear after an incubation period for two to six days. The symptoms are divided into :

1- Slight symptoms

Flu-like fever symptoms occur with acute muscle and joint pain , besides a headache, appetite loss and vomiting . Some infected people suffer from neck stiffness and sensitivity to light . The RVF symptoms usually continue for 4 to 7 days , after that an immune response begins as a result of antibodies' appearance and gradual disappearance of the virus from the blood where the problem of the disease resolves on its own (WHO , 2016) .

2- Severe symptoms

Infection progressions appear in a small percentage of human infections include :

1- Ocular form (eye injuries) (0.5 – 2 % of the patients)

The ocular symptoms , represented by retinitis , begin to appear 1-3 weeks after the first disease symptom appearance. The patients often suffer from darkening , lack of vision , or permanent vision deficit . The disease may disappear on its own without leaving permanent complications within 1-12 weeks . However , inflammation in the eye occurs as a infection progression of the disease in 1-10 persons , yet it is uncommon for patients to die .

2- Meningeal form (less than 1%)

It is a neurological symptom , an inflammation of the cerebral membranes . This form of the disease usually begins 1-4 weeks after the appearance of the first symptom of fever involving severe headaches , amnesia , hallucinations , disorientation , dizziness , disorientation and coma , moreover , neurological complications such as convulsions may develop afterward (more than 60 days later) . The death rate is lower among patients who only suffer from this form of the disease , but it is common for occurrence a neurological failure that may be severe .

3- Hemorrhagic form (less than 1%)

The symptoms of this form appear 2-4 days after the disease beginning . They involve weakness in liver function , such as jaundice, followed by signs of bleeding, including blood vomiting and stools as well as bruising, which is the presence of blood resulting from bleeding in the skin and bleeding from the nose or gums . It also causes menorrhagia and bleeding from the sites of blood withdrawal from the vein . During the pandemic that occurred in 2006 and 2007 , there were 150 reported death cases among human-caused by RVF in addition to

more than 700 infection cases ; and there was pressure on the resources and public health facilities operating in the northeastern regions of Kenya (Nguku et al , 2010) .

Infection severity and symptoms in animals

The infection severity differs from an animal to another according to the animal type and age . The infection in cattle and sheep is more severe than that in goats. It was noticed that the mortality percentage of the lambs reaches 9% while in goats is only 1%. It was also noticed that the mortality percentage of the lambs reaches 9% while in goats is only 1%. It was also observed high mortality in newborn animals; the newly imported foreign strains to endemic areas were more severely affected than the strains that had adapted to local conditions . The symptoms were abortion of pregnant females, high fever, and death in small animals, in addition to symptoms similar to influenza that infect human (Mutua et. al. 2017)

Monitoring the infection vectors

It is recommended to monitor mosquitos' some species of the genera *Culex* and *Aedes* pre and post control to guide control efforts and evaluate the effectiveness of control interactions that have an influential role in reducing the disease transmission and its effect on the mosquito's life cycle . It is also recommended to evaluate the risks and drawing risk maps as well as Carrying out analytical activities that support decision-making about control strategies that may be simple for experts who are working in the Department of Veterinary, Entomology, Meteorology and Health, and this reduces risk factors and helps in evaluating the economic and health costs in RVF-free countries . Quantitative risk mapping that shows the predictive value of several risk factors depends on where an outbreak of RVF occurs . The predictions of statistical models are presented in a GIS as map where the value of the model is calculated in each region of the RVF-prone countries. There is an example of licensed RVF maps in the East African region (Fig.2) . These maps are biased towards identifying areas likely to be exposed to the Nino phenomenon associated with RVF outbreaks(Anyumba et. al. 2010) .

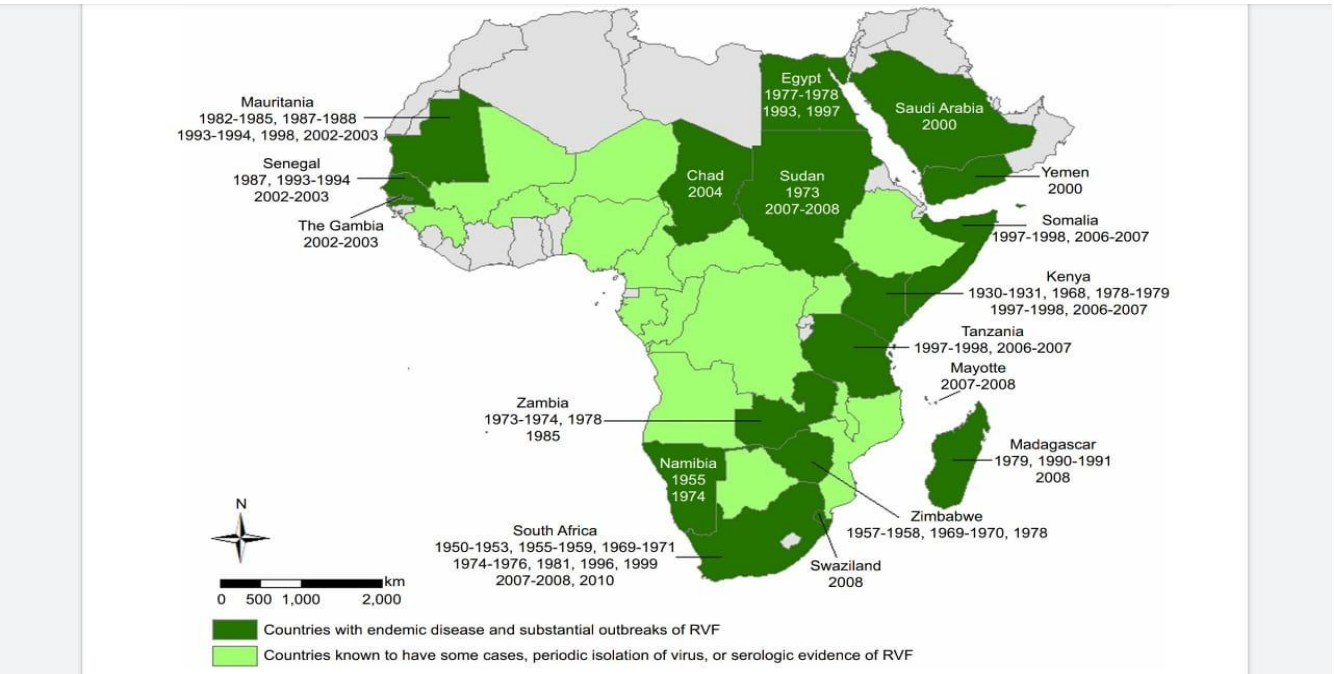

Fig 2. Geographical distribution of Rift Valley fever virus (Centers for Disease Control and Prevention, 2003)

Infection vector control

The first stage of breaking out the RVF disease is the appearance of the infected mosquitos, followed by waves of mosquitos contributing to the magnification of the infection within animal herds . Although mosquitoes and their larvae can be controlled by using insecticides in their breeding areas , this can have a long-term negative impact on the environment and living organisms ; however , good knowledge of the mosquito main focus reduces the use of pesticides. It is difficult to use chemical insecticides for controlling the larvae practically and perfectly especially when the animal husbandry sites are wide , Furthermore, using insecticides must be subjected to local and international regulations , as insects form part of the ecosystem that are active having an essential distinctive role in plant pollination that is a necessary part of the food chain . Nevertheless, detailed guidance on vector strategies and selection of appropriate insecticides is available as using insecticides in addition to repellent products reduce the risk of infection as well as lowers the risk to human (Anyumba et al 2010) .

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