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Global distribution of human chikungunya arbovirus infection: A review

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ABSTRACT

The five main arbovirus families that cause diseases in humans and other animals are Bunya viridae, Togaviridae, Flaviviridae, Reoviridae, and Rhab doviridae. Chikungunya arbovirus (Togaviridae: Alphavirus), an arbovirus transmitted by *Aedes* spp., is a well-known global health threat. It has been recognized in more than 60 countries in Asia, Africa, Europe, and the Americas. Pakistan, the eastern neighborhood of Iran, is one of the endemic foci of this disease. As the largest province of Iran, Sistan-Baluchestan has always been threatened by infectious diseases from abroad due to its geographical location and neighborhood with Afghanistan and Pakistan. Contagious diseases are more likely to occur in the eastern borders of Iran arising from (1) lack or limited jobs due to deprivation of the area, the harsh weather conditions, unbearable conditions, traditional society, and lack of industry development; (2) Lack or limited facilities due to the distance from the center of the country and high percentage of illiteracy or low literacy, and traffic to neighboring countries to trade goods and get a job. Therefore, health authorities should pay more attention to trafficking of illegal aliens, traveling of people to high-risk countries, smuggling of livestock, and strengthening of quarantine posts across borders, especially in the eastern borders of Iran. The first case of chikungunya disease was confirmed in Sistan-Baluchestan province in 2019, where most of the cases have been reported. The findings of the present study provide evidence of chikungunya virus in Iran and emphasize the urgency to increase the preventive standards and surveillance system.

KEYWORDS: Chikungunya; Epidemiology; Arbovirus; Control; Mosquito; *Aedes*; Geographical distribution; Iran

1. Introduction

According to the report of WHO, the world will face ten major health threats in 2019 including air pollution and climate change, non-contagious diseases, flu pandemic, fragile conditions (famine, drought, earthquake, population displacement, war), drug-resistant pathogens, Ebola and other very dangerous diseases (Zika, Nipah, Middle Eastern respiratory syndrome coronavirus or MERS and severe acute respiratory syndrome), poor health facilities, indifference to vaccination, AIDS, and dengue fever[1].

Approximately 49% of the pathogens and 73% of the 156 emerging diseases known are zoonoses. The zoonotic diseases are of great importance due to the high mortality rate, abundant social, economic, and health dimensions, and the creation of terror in human society. West Nile fever and Sindbis are the only two zoonotic arboviruses, and their transmission by mosquitoes has been confirmed in Iran. WHO has highlighted the possibility of outbreaks of Rift Valley fever and Japanese encephalitis due to the presence of their vectors in Iran. Rift Valley fever virus has been recently demonstrated serologically in cattle (1.7%) and sheep (2.11%) in Kurdistan province, western Iran. Dengue fever is one of the most important zoonoses and the most widely spread arboviral disease in the world[2,3].

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Vector-borne diseases account for more than 17% of infectious diseases causing more than 1 million deaths a year. Malaria causes more than 600 000 deaths worldwide each year, and most of them are children under five years old. However, most of these diseases can be prevented through conscious protective measures. More than one billion cases of vector-borne diseases are reported annually such as malaria, dengue fever, schistosomiasis, human trypanosomiasis (sleeping sickness), leishmaniasis, Chagas, yellow fever, Japanese encephalitis and onchocerciasis[4].

The import of exotic mosquito species is common in today's world. For example, over the last three decades, *Aedes albopictus* (*Ae. albopictus*), a species originally from Asia, has extended its distribution to Africa, southern Europe, the Middle East, Oceania and south, central and north America. In Iran, there is a risk of spreading mosquito-borne diseases due to the entry of exotic mosquito species from neighboring countries. Outbreaks of mosquito-borne viral diseases have been recently reported in neighboring countries of Iran, such as West Nile fever in Iraq, Rift Valley fever, and dengue fever in Saudi Arabia and West Nile fever and dengue fever in Pakistan[5].

Mosquitoes transmit many arboviruses that cause encephalitis, hemorrhagic fever, systemic febrile diseases, and polyarthralgia[5]. As a mosquito-borne arbovirus, chikungunya virus (CHIKV) is responsible for periodic and explosive outbreak of a febrile disease characterized by severe, painful, and long-term polyarthralgia. CHIKV was first identified after isolation from the serum of an infected patient during an outbreak of arthritis in Tanzania in 1952[6-9]. The disease was called chikungunya because the infected people bend themselves due to hard walking conditions. Chikungunya was derived from the Kimakonde language in Tanzania meaning "to become contorted" to describe the bent appearance of the patients with joint pain[4].

The virion of CHIKV is spherical, 70 nm in diameter while the genome size is 11.8 Kb in length, and it is an enveloped positive strand RNA virus. The viral particle is formed by 240 copies of the capsid protein and surrounded by an envelope composed of a lipid bilayer. Infection of CHIKV is spread *via* dermal macrophages and fibroblasts. When the CHIKV achieves joints, muscles, and liver, immune response is produced. Replication of CHIKV begins host immune response[10,11].

The infections of CHIKV and dengue fever are clinically indistinguishable, and the precise diagnosis of these diseases on clinical aspects is generally problematic. It has stated that a higher rate of people infected with CHIKV are symptomatic than those infected with dengue fever[12,13]. If a person is infected once and recovers from the CHIKV, he or she will be immuned to the disease for the next times. Although the disease does not cause death, the symptoms of the disease may persist for months or years. Symptoms of human CHIKV infection include several conditions such as, joint swelling, joint pain, headache, rash, fever, and muscle pain. Joint pain and fever are the most prevalent symptoms of CHIKV. Polyarthralgia is recurrent in 30%-40% of infected people. The symptoms of the disease may be severe and even lead to disability. Babies, adults over 65 years, and persons with diabetes, high blood pressure, or heart problems are at risk for more severe symptoms. The infection is self-limited and symptoms generally recover during 7-14 d[14,15].

There are two transmission cycles involved in CHIKV, the urban cycle and the forest (sylvatic) cycle. The urban and forest cycles involve man-mosquito-man and animal-mosquito-man, respectively. In the urban cycle, human and the *Aedes* spp. serve as hosts and vectors, respectively. *Ae. aegypti* is well adopted in the urban regions and is also the main vector. However, in recent years *Ae. albopictus* has been reported to cause epidemics, too. In Asia, urban cycles are predominant. The forest cycle is prevalent in Africa and is maintained between primates and *Aedes* spp. of the forest[16,17].

2. Data collection

This is a review article in which the internet, websites of accredited medical and health journals, and databases such as Web of Science, Ovid, PubMed, Systematic Review, Scirus, Science Direct, Scopus, Google Scholar, and Medline were searched using keywords such as chikungunya, mosquito-borne diseases, arbovirus, vector, *Aedes*, Culicidae, reservoir, muscle pain, global spread, epidemiology, control, endemic, diagnosis, treatment, and Iran from 1955 to 2019. A total of 100 articles were found and 96 of which were selected based on the study objective. The articles were then reviewed and criticized. Finally, the findings were prepared in the form of a review article. Various aspects of the chikungunya epidemiology were analyzed according to climatic, social, and economic conditions.

3. Symptoms

The vast majority of infected people are symptomatic, while only 3%-28% of the infected cases would remain asymptomatic. For the patients who develop the symptomatic disease, the incubation period is usually 4-8 d, but the range can be between 2-12 d. During the first week of infection, the CHIKV can be found in the patient's blood, and the transmission among humans is through mosquito bites. Therefore, preventing mosquito bites in the first week of infection can block the transmission of the disease[4,18]. Chikungunya causes a self-limiting infection in humans[19]. The most common symptoms are sudden-onset fever and joint pain. Other symptoms include muscle pain, backache, joint swelling, headache, nausea, fatigue, and rash. Joint pain is often debilitating, but most patients recover soon from joint pain within a week, while in rare cases, joint pain may last several months or years[20-23]. Ocular, neurological, cardiac, and gastrointestinal symptoms have been reported in some cases, which are often mild and may not be diagnosed or may be mistaken for other diseases such as dengue fever. Despite similar symptoms of chikungunya and dengue fever, joint and muscle pain in chikungunya is generally more severe and prolonged[24,25]. Clinical symptoms of chikungunya

infection during the early phase are often indistinguishable from that of dengue fever. Simultaneous isolation of chikungunya and dengue fever virus from patients's blood has also been reported[26]. Chikungunya contains a low mortality rate, as an approximate mortality rate of 1% has been reported for the disease[27], but its symptoms can be severe and debilitating. Infants, adults over 60 years, and people with hypertension, diabetes, and heart problems have a higher risk of severe symptoms. Mother to child transmission of chikungunya has also been reported[28].

4. Diagnosis and treatment

Rountine laboratory tests for CHIKV include serological tests and RT-PCR. The disease can be diagnosed through serologic methods such as enzyme-linked immunosorbent assay (ELISA) which is capable of detecting the presence of IgG and IgM anti-chikungunya antibodies. Blood levels of IgM reach a peak within 3-5 weeks after the disease onset and last about 2 months. Both serologic and virologic methods should be used in the first week after the disease onset. The virus can be isolated from patients within the first few days of infection. Different reverse transcription-polymerase chain reaction methods are accessible, but validity information are limited and have variable sensitivity[18,29]. Meanwhile, immunofluorescence assays, plaque reduction neutralization tests and haemagglutination-inhibition tests are useful, sensitive and specific for diagnosis of CHIKV[30].

There is no specific antiviral medicinal treatment or vaccine for chikungunya, but available treatments can relieve the symptoms. Complete rest, drinking fluids, and prescribing analgesics and antipyretic medicines are recommended[31-33]. Chloroquine is as a possible treatment for the symptoms related to infection, and as an anti-inflammatory agent to control the arthritis related to CHIKV[30].

5. Vectors and reservoirs

Chikungunya virus is an RNA virus of the Togaviridae family and of the *Alphavirus* genus. The disease is transmitted to humans through the bites of infected female *Aedes* species mosquitoes. The mosquitoes' peak activity is in the early morning and late afternoon. *Aedes* mosquitoes are widely distributed throughout the world, and some are vectors of other important arboviral diseases such as dengue fever, yellow fever, West Nile fever, and Zika. Diseases transmitted by *Aedes* mosquitoes are far more dangerous and deadly than malaria transmitted by *Anopheles* mosquitoes. *Aedes* mosquitoes are dangerous health-threatening pests because of their blood-feeding behavior and persecution of humans and animals as well as the transmission of arboviral diseases[34-36].

Chikungunya emerged in 1952 in an area called Makonde between Tanzania and Mozambique and spread rapidly throughout the world. This pathogenic virus was first isolated by Ronald Ross in a febrile patient from the Nawala region of Tanzania[7-9,37]. The wild cycle of this virus is formed in forest monkeys and mosquitoes. The virus, of African origin, was later introduced into Asia and subsequently transmitted from human to human by *Ae. aegypti* mosquitoes. *Ae. aegypti* is the main vector and *Ae. albopictus* became the second vector in the urban cycle of chikungunya[38-40]. *Ae. aegypti* is limited to the tropics and subtropics, while *Ae. albopictus* has been found in temperate and even cold temperate areas, although they have been found in other continents due to climate change, global warming and other reasons in recent decades. Both *Ae. aegypti* and *Ae. albopictus* are invasive and container-breeding. *Ae. aegypti* mainly feed on humans and rests indoors. *Ae. albopictus* periodically feeds from humans and animals and tends to rest outdoors, but it has a high anthropophagic behavior. Both species feed outdoors, but *Ae. albopictus* feeds easily indoors too[41,42]. In Africa, several other species of mosquitoes including *Ae. furcifer/taylorigroup* and *Ae. luteocephalus* have been reported as vectors of the disease[6]. The virus is thought to be maintained in nature in a sylvatic transmission cycle in arboreal primates. However, other species may also be involved as reservoirs. Evidence shows that non-human primates, rodents, birds, and small mammals can be reservoirs of the disease. In addition, reptiles and amphibians have also been identified as the potential reservoir hosts of CHIKV[6,43].

6. Epidemiology

After the outbreak in Tanzania, CHIKV caused an epidemic during 1960-1990 in east, west, and central Africa, including Uganda, Zimbabwe, Senegal, Central African Republic, Congo, and Cameroon[44-46]. The virus was also found in Portugal, Guinea, the Philippines, Malaysia, Mayotte, and the Reunion Islands. The first report of the disease in Asia can date back to 1958[47]. The outbreak of the disease in Africa and Asia was unpredictable; two consecutive epidemics occurred with an interval of 7 and 20 years. In India, the outbreak occurred in Calcutta from 1963 to 1964 and in Madras in 1965[48-51]. Despite the unknown origin of CHIKV in India, it is believed that the disease may have been introduced to Calcutta, one of the biggest cities of India, through sea or air[52]. Among the megacities, Bangkok has been recognized as an active area of disease transmission[53-55]. Outbreaks from Cambodia, Laos, Vietnam, and Myanmar have been also documented[56]. In 2004, a major epidemic of CHIKV occurred in east, west, and central Africa, beginning from Kenya, then continuing in 2005 to Comoros, Reunion, and other islands in the southwestern Indian Ocean. About 266 000 cases of chikungunya (34% of the population) were reported in the Reunion Island[57,58]. Then, an epidemic with the same strain of the virus hit the Indian subcontinent in 2005-2006, affecting more than 1.5 million cases[59]. The virus was mutated in the Reunion epidemics and was able to adapt to *Ae. albopictus* and then spread to India and northeastern Italy[60-62]. Cases of chikungunya have

also been reported in the UK, Belgium, Germany, the Czech Republic, Norway, Spain, France, Canada, Sri Lanka, China, and the United States. These cases were directly associated with the passengers from India and the Indian Ocean Islands[47,63]. Since 2011, when the virus was first detected in the Pacific Island region of New Caledonia, CHIKV has spread to 10 of the 22 countries and territories in the Pacific region, the strains of which had Asian ancestry and was responsible for the majority of cases[64-66]. Since the beginning of 2012, the Oceanic Islands have faced not only CHIKV but also epidemics of dengue and Zika viruses[67,68]. Like dengue virus and Zika virus, infected travelers from Pacific are thought to be the main source of CHIKV. The Asian strains were responsible for the disease in the Indian subcontinent, Southeast Asia, and Oceania[69-74]. With such huge number of CHIKV imports through the infected travelers, its introduction to the western hemisphere seemed inevitable. In December 2013, the first local transmission of CHIKV (local transmission means that mosquitoes in the region have been infected with the virus and are spreading it to people) in the western hemisphere was reported, and then indigenous cases were detected in the Caribbean island of French St. Martin[75]. The emergence of CHIKV in the western hemisphere was noteworthy as the virus rapidly spread to native populations in the Caribbean as well as in central, south, and north America. Since the introduction of CHIKV in the United States in 2013, more than 2 million suspected cases from endemic areas have reported in approximately 50 countries[76]. The risk of CHIKV is high in the tropical regions of the US.

The establishment of CHIKV in the United States, as well as recurrent events, indicate that the virus will continue to spread, and the sporadic and explosive outbreaks of CHIKV observed in Africa and Asia are likely to occur in the western hemisphere[77]. The disease has been diagnosed and spread in more than 60 countries in Asia, Africa, Europe, the Americas and Oceania by September 2019[63].

According to the statistics released by WHO, 2.5 billion people live in dengue fever and other viral diseases striking areas. Numerous outbreaks of dengue fever and chikungunya have recently occurred in various countries including Iran's eastern neighbor, Pakistan[78,79]. Like other mosquito-borne viral diseases such as yellow fever, Zika, and West Nile fever, chikungunya is rapidly expanding worldwide, and it is an important threat to public health[80,81]. International travel is blamed for the global spread of CHIKV. Other factors contributed to its global expansion include the emerging of new vectors, globalization, climate change, and global warming, *etc.* This situation is especially dangerous in countries with shared borders with countries where the disease vectors have been previously colonized[82]. The largest outbreak of CHIKV with a high rate of CHIKV infection of 70% (411/584), among suspected cases in South Asia occurred in Pakistan during 2016-2017[83]. Considering the long border of Sistan-Baluchestan province with Pakistan, CHIKV can enter from Pakistan to Iran. Like other viral diseases, CHIKV has recently been introduced as a health emergency by WHO; therefore, there is an increased need for attention to the disease in Iran.

7. Control

To control the disease, the number of household larval container (water storage tanks, containers, and ornamental plants) and rain-filled larval (used tires and cavities) should be reduced. During the outbreaks, adult or immature mosquitoes should be killed with insecticides. In addition, repellents can be applied to exposed skin or clothing and full-body coverage (long pants and long sleeves). The use of mosquito coils and other easily sublimated insecticides may be effective in reducing the number of mosquitoes indoors. Insecticide-treated nets can be also used during resting throughout the day[6].

8. Situation in Iran

In a study, a total of 159 serum samples of Iranian patients suspected of chikungunya infection were studied from April 2017 to June 2018. Coming from Chabahar, Iranshahr, Konarark, Mirjawa, Ghasre-e Ghand, Rask, Saravan, Sarbaz, Zabol and Zahedan Counties in Sistan-Baluchestan province in southeastern Iran (neighboring Pakistan), these patients with clinical manifestations of fever and arthritis were examined for chikungunya infection. The patients were studied through both serological and molecular methods and finally, 40 CHIKV-positive cases (25.2%) were found. Most of the positive cases (65%) were the residents of Sarbaz county in the eastern Sistan-Baluchistan province. This report confirmed the existence of the disease in Iran[84]. According to the literature, these cases are imported, and chikungunya is expected not only to be endemic in Sistan-Baluchestan province but also to expand to the neighboring provinces in the near future[61].

A total of 69 species of mosquitoes of the family *Culicidae* have been reported In Iran, of which 39 species belong to the subfamily *Culicinae*, and 12 species to the genus *Aedes*. *Ae. albopictus*, as a vector of CHIKV, has been reported in Iran. There are 7 or 11 genera depending on the generic classification of the tribe Aedini[85-94]. Iran has a favorable climate for endemic transmission of arboviruses by *Aedes* mosquitoes[95]. Immigrants from neighboring countries can increase the risk of disease transmission in Iran. Choosing high-risk countries, especially east Asia, as destination, these Iranian passengers, are at the risk of chikungunya infection. Besides, traveling to the areas where CHIKV is active may increase the risk of chikungunya transmission to Iran. The risk of CHIKV transmission is higher in the summer when Iranians travel more often[96].

Sistan-Baluchestan province in Iran has always been at risk for infectious diseases due to its geographical extent and having more than 600 km of common earth-water border with Pakistan. On the other hand, low health indicators and the lack or limited health

facilities in the neighboring eastern countries have caused a number of arboviruses to enter the country each year and threaten the southeast and subsequently the rest of Iran. In addition, the poor economic situation in southeast of Iran (due to lack of facilities and jobs which lead to illegal activities such as fuel smuggling and travel to neighboring countries) has increased the possibility of communicable diseases. In this regard, the health authorities are recommended to emphasize stricter surveillance, strengthen quarantine posts in the eastern borders and raise awareness of people as well as health staff and healthcare providers.

Conflict of interest statement

The authors report no conflict of interest.

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Authors' contributions

All authors participated in the research design and contributed to different parts of the research.

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