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A Review on Epidemiology, Diagnosis and Treatment of Chikungunya Virus

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Abstract:

Chikungunya virus is a mosquito-transmitted alphavirus that causes chikungunya fever, a febrile illness associated with severe arthralgia and rash. Chikungunya virus is transmitted by culicine mosquitoes; Chikungunya virus replicates in the skin, disseminates to liver, muscle, joints, lymphoid tissue and brain, presumably through the blood. Chikungunya is a viral disease transmitted to humans by infected mosquitoes. Like most mosquito-borne infections, the virus can only be transmitted by blood-to-blood contact, through a mosquito bite or transfusion with infected blood. The disease is characterized by the common symptoms involving rashes, nausea and headache. In addition to this, it also causes intense joint pain and fever, which is known as arthralgia. It is widely spread in America, Africa and all over the world. The onset of chikungunya fever is more intense and the period of illness is shorter than that of dengue fever. Recently, chikungunya has become a serious public threat. The chikungunya symptoms are usually self-limiting and prophylactic treatment is currently unavailable to cure the disease, although various allopathic medicines, such as NSAID's, analgesics, steroids, DMARDs and some anti-viral drugs claim to treat the disease. However, these medicines provide only symptomatic relief with serious side effects. Nowadays, researchers focus more towards an alternative treatment. The present review aims to highlight the epidemiology of chikungunya, treatment options available, and potential of alternative medicines for its treatment.

KEYWORDS: chikungunya; alphavirus; immunopathology; monoclonal antibodies; antivirals; pathogenesis, virus receptor, vaccine, immunopathogenesis, epidemiology.

INTRODUCTION:

Chikungunya is a mosquito-borne illness of humans caused by the chikungunya virus (CHIKV) that belongs to The Alphavirus genus of the family Togaviridae.(1) The disease Is transmitted by Aedes aegypti and Aedes albopictusMosquitoes which are the main vectors of chikungunya in Asia and the Indian ocean islands. The name "chikungunya" is a descriptive term used by the local Tanzanian Makonde people to describe the disease and can be translated as "disease that bends up the joints".(2)

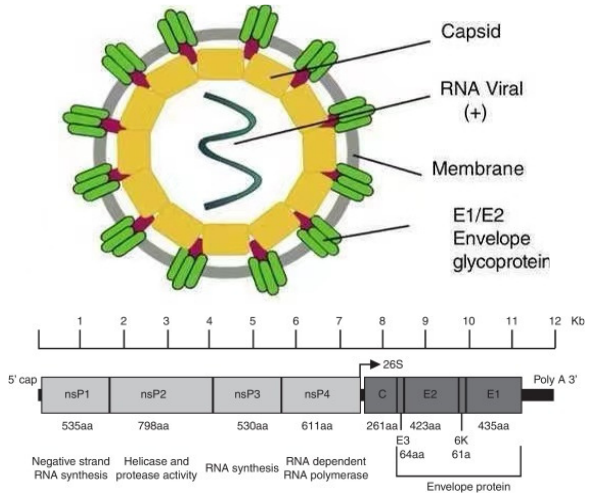

Fig.1 structure of chikungunya virus and organization of Chikungunya virus genome

Chikungunya virus is an enveloped plus-strand RNA virus with icosahedral symmetry. The virion is 70nm in diameter and it is composed of repeating units of the E1 and E2 transmembrane glycoproteins (240 heterodimers of E2/E1 arranged as trimeric spikes on its surface), the capsid (C), a host-derived lipid bilayer, and a single molecule of genome RNA. The genome is approximately 12kb in length and encodes the nonstructural proteins (nsPs) at the 5′ end and the structural proteins at the 3′ end. The nsPs are translated from genomic RNA and the structural proteins from a sub genomic RNA.(3)

Alphaviruses enter target cells by endocytosis. A few receptors (DC-SIGN, L-SIGN, heparin sulphate, laminin and integrins) have been implicated in this process, but their precise roles have not been clearly proven. Recently, prohibitin was identified as CHIKV receptor protein. Following endocytosis, the acidic environment of the endosome triggers conformational changes in the viral envelope that expose the E1 peptide, which mediates virus–host cell membrane fusion. This allows cytoplasmic delivery of the core and release of the viral genome.(4) Two precursors of non-structural proteins are translated from the viral mRNA, and cleavage of these precursors generates nsP1–nsP4. These proteins assemble to form the viral replication complex, which synthesizes a full-length negative-strand RNA intermediate. This serves as the template for the synthesis of both sub genomic (26S) and genomic (49S) RNAs.The sub genomic RNA drives the expression of the C–pE2–6K–E1 polyprotein precursor, which is processed by autoprotolysis.(5)

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The capsid is released, and further processing generates the pE2 and E1 glycoproteins. PreE2 and E1 associate in the Golgi and are exported to the plasma membrane, where pE2 is cleaved into E2 and E3. Binding of the viral nucleocapsid to the viral RNA and the recruitment of the membrane-associated envelope glycoproteins promote viralassembly.The assembled alphavirus particle, with an icosahedral core, buds at the cell membrane. (6)
The disease typically consists Of an acute illness with fever, skin rash, and incapacitating Arthralgia. The disease may evolve into three phase. The Acute phase is from day 1 to day 21. The sub acute phase is From day 21 to day 90. The chronic phase starts from 3Months to onwards. For the following 50 years (approximately) after its initial isolation, CHIKV caused only occasional outbreaks in Africa and Asia.(7) Although CHIKV mortality rates are low, this virus imposes pronounced morbidity resulting in a substantial impact on the quality of life of infected individuals and significant economic losses, especially in developing countries. In the vast majority of individuals, CHIKV infection is characterized by an abrupt onset of fever, frequently associated with joint pain. Other symptoms are also reported, although to a minor extent, and these may include incapacitating polyarthralgia and arthritis, rash, myalgia, and headache. Asymptomatic CHIKV infections do occur but are rare and estimated at about 3 to 28% of the infected individuals, varying between different epidemic outbreaks.(8) Acute symptomatic CHIKV disease resembles other common well-known arbovirus-induced diseases, such as dengue fever caused by the dengue virus (DENV) and the Zika virus (ZIKV) disease, which are frequently inaccurately diagnosed given the simultaneous circulation of the different viruses in the same location, making diagnosis challenging. (9)Although the infection is usually a self-limited disease, some patients develop persistent joint pain that may last for months or years after the acute phase of disease. A recent Indian study reported transmission of Chikungunya virus by Anopheles stephensi too. The Indian Ocean outbreak is caused by transmission by Aedes only. The common reservoirs for chikungunya virus are monkeys And other vertebrates. The role of cattles and rodents has Also been reported in the transmission of the virus.The CHIKV usually shows a periodicity with occurrence Of disease in the community with latency intervals of 3-4 years, probably due to its cycle in monkeys. (10)Following transmission.CHIKV replicates in the skin,and Dissemination to the liver, muscle, joints, lymphoid tissue (lymph nodes and spleen)and brain, presumably through the Blood.
CHIKV spreads rapidly in the body after initial infection. Following inoculation with CHIKV through a mosquito bite, the virus directly enters the subcutaneous capillaries, with some viruses infecting susceptible cells in the skin, such as macrophages or fibroblasts and endothelial cells.(11) Local viral replication seems to be minor and limited in time, with the locally produced virus probably being transported to secondary lymphoid organs close to the site of inoculation. Virus dissemination through the blood and pathological events associated.(12)True arthritis remains a rare event (from 2% to 10%). The pathological events associated with tissue infection are mostly subclinical in the liver (hepatocyte apoptosis) and lymphoid organs (adenopathy), whereas in the muscles and joints are associated with very strong pain, with some of the patients presenting arthritis.

VECTORS, TRANSMISSION AND RESERVOIRS:
Chikungunya virus is transmitted by Aedes mosquitoes (Ae.Aegypti & Ae. albopictus) which breed in clean water collections in containers, tanks, disposables, junk material in domestic and peri-domestic situations besides natural habitats like tree holes, plantations etc. Like Dengue its transmission is also related to rainfall and temperature. In recent years, it has been observed that during the period of monsoon and post-monsoon there is an upsurge in the cases because population of the vector fluctuates with rainfall and its life span is influenced by temperature and humidity. (13)
A high vector density in the post-monsoon season enhances virus transmission. The transmission cycle are divided into enzootic and urban. In Africa, an enzootic cycle occurs in forested habitats where arboreal mosquitoes, principally Aedes spp, serve as vectors. Evidence points to nonhuman primates as the principal reservoir and amplification host in enzootic cycle whereas human are the host during epidemics. (Fig.2) The enzootic transmission cycle can spill over to infect people who live nearby, and enzootic mosquito vectors may be involved in interhuman transmission during small outbreaks. Epidemics also occur in Africa when CHIKV is introduced into urban areas where the more anthropophilic vectors, Aedes aegypti and Aedes albopictus, can initiate human—mosquito—human transmission.(14) The endemic/epidemic cycle results in high levels of human exposure to mosquito transmission, particularly because these vectors live in close proximity to people. Aedes aegypti is the main vector of transmission of Chikungunya in Bangladesh. However, Aedes albopictus has been found to be playing a part in some areas. They are principally day biters. Eggs of these vectors have the ability to withstand desiccation for more than a year. This could result in the virus to remain in nature for long periods and cause outbreaks. Flight range of these vector mosquitoes are less making the outbreaks to occur in clusters, especially in congested localities.(15) Recently, it has also been shown that viraemia are quite high and infected mosquitoes could transmit the disease to more than one person since small amounts of blood in the proboscis still carry large quantity of virus. Aedes mosquitoes take multiple feeds per day and it would also result in small focal outbreaks. In the initial part of outbreak, individual population is not protected which could result in larger outbreaks. The aedes aegypti adult females prefer to feed on humans, often take several partial blood meals during a single gonotrophic cycle, ovipo sit in artificial containers as their preferred larval sites, and rest inside houses with ready access to human hosts. A. albopictus is both zoophilic and anthropophilic, aggressive, silent, active all-day long, and has a longer lifespan than other mosquitoes (up to 8 weeks). (16)
In recent decades it has expanded to several areas previously known to be Aedes-free. It seems that most new introductions of A. albopictus have been caused by vegetative eggs contained

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in timber and tires exported from Asia throughout the world.The human infections are acquired by the bite of infected Ae. aegypti /Ae. Albopictus mosquitoes, which are day biters and epidemics are sustained by human-mosquito-human transmission.

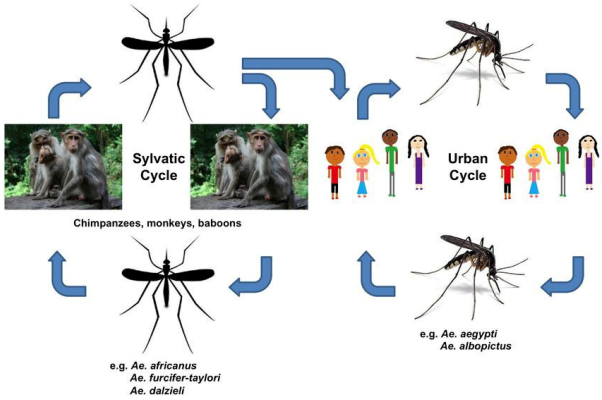


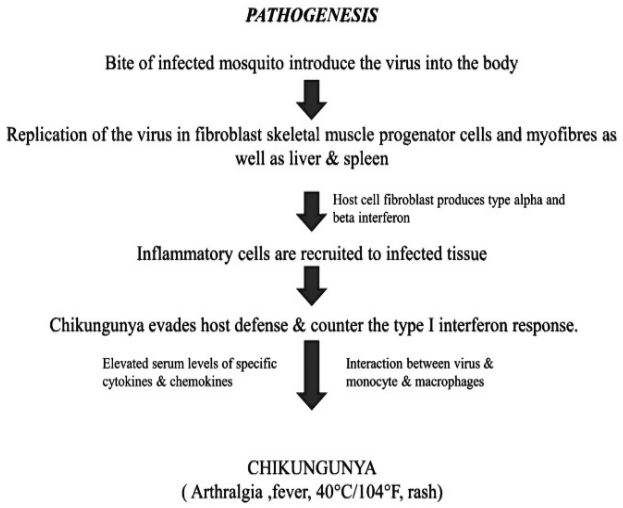
Fig.2 The sylvatic cycle reside in primates but during outbreak the urban cycle consists of man mosquitoe man cycle

EPIDEMIOLOGY:

The first reported epidemiological cases of fever, arthritis, and rashes resembling the CHIKF include cases in Zanzibar (Africa) in 1823, and an epidemic on the island of Saint Thomas (Caribbean) in 1827 and 1828.Some authors propose that the spread of the CHIKV beyond African territory may have begun in the mid-18th century when sailing ships carried humans and infected *Ae. aegypti* mosquitoes in sufficient numbers for the virus to circulate on board the ships, where the water stored for the crew was conducive to the reproduction and propagation of mosquitoes. However, it was not until 1952 that the CHIKV was isolated from the serum of a febrile patient during an outbreak on the Makonde plateau, located in south-eastern Tanzania in East Africa; and in 1953, it was isolated for the first time from *Ae. aegypti* mosquitoes, one of the main vectors of this virus.(17)Based on the disabling and debilitating symptoms presented by patients with severe arthralgia, the disease was given the name "Chikungunya".Including Philippines (1954, 1956 and 1968), Thailand, Cambodia, Vietnam, India, Myanmar and Srilanka. The re-emergence of CHIKV infection was also found in democratic Republic in Congo in 1999-2000, Java in 2001-2003 and in the islands of South western Indian ocean i. e Myotte, Seychilles and Mauritus.(18) 13 Imported cases from these islands were found in Europe in the beginning of 21st century. According to Euro- surveillance, 2006; 307 cases were found in France, 197 in Italy, 17 cases in Germany, 9 in United Kingdom, 12 in Belgium and 1 in each Czech Republic and Norway.3,12,13 CHIKV arrived in the America in 2013. From March, 2013 to March, 2016 approximately two million cases of Chikungunya virus infection have been reported in South American regions including Brazil, Columbia, Venezuela etc. In Brazil, the virus was first identified in 2014 and thousands of people became infected. In the Indian sub-continent, first isolation of the virus was done in Kolkata in 1963 followed by several reports of CHIKV infection in different parts of India during 1960s. The first outbreak occurred in India in 1973. Then after a long inter-epidemic, period of three decade, again in 2006, a large scale outbreak of Chikungunya fever took place.14 The incapacitating arthralgia raised the doubt about the infection in the early period of 2006. The diagnosis was confirmed as Chikungunya virus infection with laboratory findings. (19)During 2006, a total of 13,90. 322 clinically suspected cases of Chikungunya infection were reported from 16 states of India, which came down to an amount of 27,553 cases in 2015.15,16 It confirmed the re-emergence of this virus in this sub-continent. It may be multifactorial, which includes social, environmental, behavioral and biological factors. In 2016, a big CHIKV epidemic affected our neighboring country India which compelled their public health system to formulate guideline to manage acute Chikungunya cases and their sequel.

PATHOGENESIS:

The pathogenesis of CHIKVD is complex and involves a combination of viral factors, host immune responses, and interactions with specific cellular factors and pathways.(20) Adding to the complexity of the CHIKVD process, the host immune response is required to clear infection, but also contributes to the pathogenesis of CHIKV-induced disease.This section will discuss the pathogenesis of CHIKV, how the host responds to infection, and the different mechanisms by which CHIKV evades the immune response.(21)



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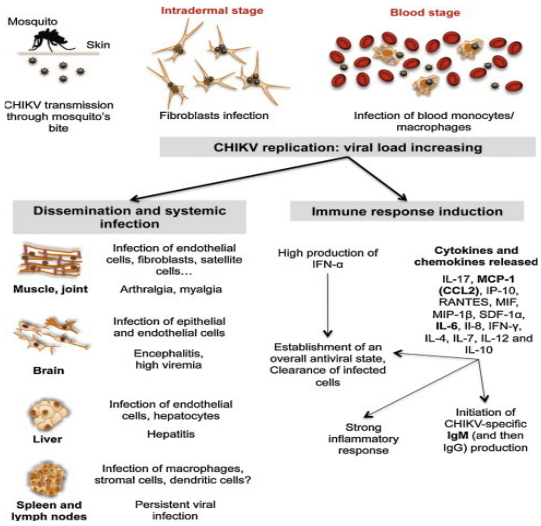

Fig.3 pathogenesis of chikungunya virus

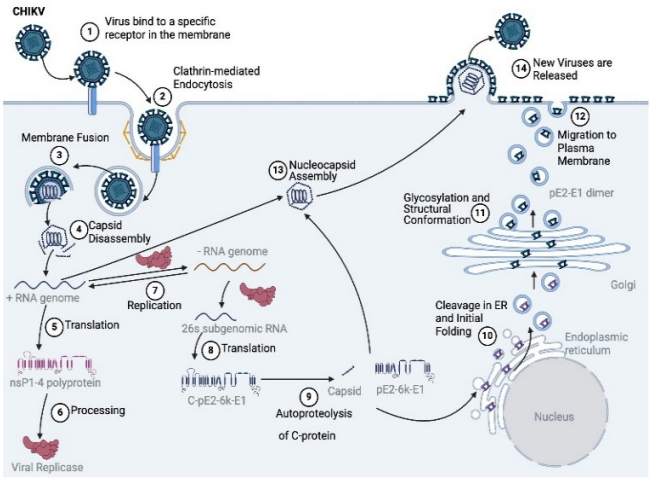

Fig.4 Replication cycle of chikungunya virus

CLINICAL MANIFESTATIONS

Acute Phase:

- Fever
- Joint pain (polyarthralgia)
- Headache
- Muscle pain (myalgia)
- Rash
- Fatigue

Chronic Phase:

- Persistent joint pain (up to 90% of cases)
- Joint stiffness
- Fatigue

DIAGNOSIS:

Chikungunya infection is diagnosed on the basis of clinical, epidemiological and laboratory criteria. An acute onset of fever and severe arthralgia or arthritis that is not explained by other medical disorders is considered a possible CHIKV case. Three main types of laboratory tests are used for diagnosing CHIKV infection: virus isolation, reverse transcriptase-polymerase chain reaction (RT-PCR), and serology.(22)

Virus isolation can be performed on field collected mosquitoes or acute serum specimens (≤8 days). Serum obtained from whole blood collected during the first week of illness can be inoculated into a susceptible cell line or suckling mouse at a reference laboratory. This can be achieved if the sample is transported cold (between 2°C and 8°C or dry ice) and as soon as possible (within 48h). Several RT-PCR assays for the detection of CHIKV RNA have been published. Real-time, closed system assays should be used, due to their increased sensitivity and lower risk of contamination. (23)Taking into account the sensitivity, PAHO recommends the use of the CHIKV RT-PCR protocols from the Centers for Disease Control and Prevention and the Institute Pasteur. Serum from whole blood is used for PCR testing as well as virus isolation.

For serological diagnosis, serum obtained from whole blood is used in enzyme-linked immunosorbent assay (ELISA). The serum (or blood) specimen should be transported at 2–8°C and should not be frozen. Serologic diagnosis can be made by demonstration of IgM antibodies specific for CHIKV or by a four-fold rise in IgG titer in acute and convalescent specimens. (24)

The determination of IgM can be made by different commercially available techniques. However, it should be taken into account that the best sensitivity is from techniques that use the complete virus as antigen compared to those that use recombinant proteins. Since the first commercially available kits had poor results, it is recommended that in house techniques for IgM/IgG ELISA be implemented using the purified viral antigen and following the CDC protocols. Recent ELISA assays have improved sensibility and specificity as shown in Table.1. The use of rapid tests is not recommended.(25) The second sample for serological determination should be taken between 1 and 2 weeks after the first sample. Seroconversion can also be detected as an increase in IgG by a factor of 4 or more between acute-phase and convalescent-phase serum samples.

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Table 1.Accuracies and sensitivities of different chikungunya fever diagnostic assays.

Assay	Sensibility (%)	Specificity (%)	PPV (%)	NPV (%)
RT-PCR	88.5	100	100	97.5
Standard Diagnostics Chikungunya IgM ELISA	3.9	92.5	10	81.6
Novatech Chikungunya IgM Capture ELISA	76.9	91.9	100	97.5
Novatech Chikungunya IgG Capture ELISA	80	100	100	95.6

THERAPEUTIC MANAGEMENT:

The growing disease burden and the risk of global outbreaks, coupled with the lack of specific treatments, have driven the development of targeted therapies. Emerging therapeutic strategies seek to interfere with viral replication, modulate the host immune response, or attenuate long-term inflammatory complications. (26)These approaches include antiviral agents, polyclonal and monoclonal antibodies, and therapeutic vaccines, many of which are still in preclinical phases or in early clinical trials.

Antiviral Agents:

Antiviral Agent	Description
Efavirenz	HIV drug, inhibits CHIKV replication
Sofosbuvir	HCV drug, effective against CHIKV
Ribavirin	Guanosine analogue, limited efficacy
Favipiravir	Pyrazine carboxamide derivative, effective against CHIKV

Antibodies

Technology	Antibody	Model	Mechanism of Action
Polyclonal Antibodies	CHIKVIg	In vivo: IFN-α/βr$^{-/-}$129s/v and C57BL/6 mice	It neutralized the CHIKV, prevented disease, inhibited viremia and clinical signs. In neonates, it reduced mortality, viral load and symptoms
	Anti-CHIKV Hyperimmune Immunoglobulin	In vivo: Human (Phase I and II Clinical Trials)	No results so far
Monoclonal Antibodies	Anti-MXRA8	In vitro: Vero cells, NIH-3T3, MEFs, HEK293T, A549, HeLa, MRC-5, HFF-1, Hs633T, Huh-7, RPE, JEG3, U2OS, HT1080, Raji and K562	Blocked CHIKV infection
		In vivo: C57BL/6J mice	Reduced viral load and clinical signs of infection
	DC2.112 and DC2.315	In vitro: Vero cells and human PBMCs	Low neutralization. Inhibited viral release and recruited myeloid cells to promote phagocytosis of infected cells

Table.2 Main studies under development with polyclonal and monoclonal antibodies against Chikungunya virus.(27)

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Vaccines:

There is currently no commercial vaccine for CHIKV, although some candidate vaccines have been tested in human beings. Several technologies have been used to develop CHIK vaccines, including inactivated viral vaccines, live-attenuated viruses, alphavirus chimeras, recombinant viral vaccines, consensus-based DNA vaccines, recombinant subunit vaccines and more recently, a virus-like particle (VLP) vaccine. Two vaccine candidates have finished phase I trials: a live recombinant measles-virus-based chikungunya vaccine and the VRC-CHKVLP059-00-VP, VLP vaccine. (28)The live recombinant measles-virus-based chikungunya vaccine had good immunogenicity, even in the presence of measles immunity, was safe, and had a generally acceptable tolerability profile. The VLP vaccine, VRC-CHKVLP059-00-VP was also immunogenic, safe, and well tolerated.

Prevention and control:

Avoidance of mosquito bites offers the best protection against CHIKV infection. Patients suspected of having CHIKV infection should avoid getting mosquito bites during the first week of illness to prevent further transmission to mosquitoes, that may in turn infect other people. The main method to reduce transmission of CHIKV is through control of the mosquito vectors and reduction of mosquito breeding sites. This requires mobilization of communities, who are critical in reducing mosquito breeding sites through emptying and cleaning containers that contain water on a weekly basis, disposing of waste, and supporting local mosquito control programmes.(29)

During outbreaks, insecticides may be sprayed to kill flying adult mosquitoes, applied to surfaces in and around containers where the mosquitoes land, and used to treat water in containers to kill the immature mosquito larvae. This may also be performed by health authorities as an emergency measure to control the mosquito population.

People living in or visiting areas with CHIKV transmission are advised to wear clothing that minimizes skin exposure to the day-biting mosquitoes. Window and door screens should be used to prevent mosquitoes from entering homes. Repellents can be applied to exposed skin or to clothing in strict accordance with product label instructions. Repellents should contain DEET, IR3535 or icaridin.

Insecticide-treated mosquito nets should be used against day-biting mosquitoes by persons who sleep during the daytime, for example young children, sick patients or older people.(30)

CONCLUSION:

The arrival of CHIKV to America will be a challenge to the public health system and a significant economic burden. The probability of autochthonous transmission in the rest of Mexico and USA is high due to the vector ubiquity. Economic development does not protect countries from vector-borne diseases; modern lifestyles may amplify an epidemic through travel, population aging, and production of solid waste that can shelter *Aedes* mosquitoes.

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