Zika Virus: A Compendium of the State of Knowledge

Chapter · September 2018

DOI: 10.1016/B978-0-12-409548-9.11019-X

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University of Santiago, Chile
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Zika Virus: A Compendium of the State of Knowledge

Alberto J Alaniz, Center for Spatial Ecology and Environment - Ecogeografía, Santiago de Chile, Chile

Introduction

Zika virus (ZIKV) is a member of the genus *Flavivirus* of the family Flaviviridae, which encompasses other important viruses such as Dengue (DENV), West Nile Virus (WNV), Yellow fever (YFV), and Japanese encephalitis (JENV). It is considered an emergent virus which generated a global health alarm during summer of 2015–16, mainly due to its association with serious clinical effects such as microcephaly and Guillain Barré Syndrome (GBS), in addition to the difficult control of its mosquito vectors in endemic areas. Despite its recent global spread, the virus was first isolated in 1947 in the Zika rainforest of Uganda, in a rhesus monkey host of a YFV control program. The first human infection was detected in Nigeria in 1954, however that case has been questioned as a misdiagnosis by Spondweni. In 1962 the first human infection was confirmed in Africa, while it has been estimated that the virus has been present in Asia since 1950. Since that year there were very few confirmed cases until the first epidemic outbreak in 2007, with just around 20 confirmed cases during this period. This low detection of cases has been attributed to the similarity of the serological and clinical presentation to other phylogenetically related viruses such as DENV.

During the last decade there was a significant increase in the virus spread and the number of cases; there were three main epidemic outbreaks from 2007 to 2015. The first outbreak occurred on the Yap Islands in the Occidental Pacific Ocean (2007), with 49 confirmed and 59 probable cases. The second outbreak was in French Polynesia in the Central Pacific Ocean (2013–14) with 340 confirmed cases. The largest outbreak began in Brazil and spread across South America, Central America, and the Caribbean, with 137,288 confirmed and another 231,725 suspected cases in Brazil between 2015 and 2018. The confirmed number of cases between 2015 and January of 2018 in America reached 223,477 cases; there were 3720 congenital syndrome cases associated with ZIKV infection worldwide. Although ZIKV has been relatively controlled, the study of this virus is currently related to issues such as new treatments and vaccines, new potential secondary vectors, the infection cycle associated with new reservoirs, their neurological and congenital effects and the efforts on prevention. The present chapter presents an up-to-date review of ZIKV state of the art, addressing biogeography, infection pathways, microbiology of the virus, clinical presentation, diagnosis, treatment, prevention, control, and future perspectives about ZIKV.

Biogeography of ZIKV

At present ZIKV has a global distribution, concentrated mainly in tropical and subtropical regions. The geographic distribution of endemic infection is determined by the presence of *Aedes* mosquito vectors, while imported cases have occurred outside this range. Phylogenetic studies have identified two main linages of ZIKV, the initial linage coming from Africa and a second linage from Asia. The source of the virus was probably East Africa, spreading to the rest of Africa and then to Asia. This Asian linage was probably spread to Polynesia in the Pacific Ocean and to the Americas during the last 10 years. The Yap Islands outbreak in 2007 was produced by a ZIKV strain introduced into Southeast Asia from Uganda and Senegal. The outbreak in French Polynesia was probably produced by an introduction from Thailand and Cambodia in 2012–13. Finally, the introduction to South America is associated with the arrival of a ZIKV strain from American Samoa, Fiji or French Polynesia in 2015, first colonizing Brazil, Haiti, and Venezuela. Since that first event of colonization the virus has spread to Martinique, Mexico, Guatemala, Dominican Republic, and the rest of America. The main cause of the rapid geographic spread during the last 10 years is related to globalization and the increase in the frequency of travel to endemic zones. The main cause of the increase in the success of the recent introduction events has been associated with changes and mutation in the Asian virus strain in America and Pacific islands, improving the capacity of the virus to spread into other regions. The main hypothesis about the ZIKV introduction that lead to the outbreak in Brazil is associated with the increase in travel from all parts of the world to Brazil during the Confederations Cup and FIFA World Cup in 2014. In America the autochthonous distribution of ZIKV includes 38 countries in Central America and the Caribbean, 8 territories in South America and two territories in North America (United States and Mexico). In Africa 30 territories have been declared at high risk; 11 of them had active transmission in December 2017. In Asia 14 territories are under risk (Fig. 1A).

Infection Pathways

The main infection pathway of ZIKV corresponds to vector-borne transmission, however perinatal transmission (mother to child), sexual transmission, and more recently blood transfusion have been reported as other infection pathways.

Vector-Borne Transmission

The main route of ZIKV infection is through the bite of a mosquito within endemic areas of infection. The primary vector of ZIKV is *Aedes aegypti* (Diptera: Culicidae) a hematophagous and globally distributed mosquito of the subgenus *Stegomyia* (Figs. 1B and 2). The female is the main source of infection, associated with blood feeding on humans in residential areas during diurnal hours. This mosquito may be identified morphologically by a series of transverse white bands on the body and black color, and no emission of sound in flight. Another mosquito attributed as a potential vector of the virus is *Ae. albopictus*, which has a similar distribution to *Ae. aegypti*; this vector may be important in subtropical regions such as Southern Brazil, Gabon, and New Caledonia, among others. Other *Aedes* mosquitoes have been identified as potential vectors for ZIKV in more restricted areas, such as *Ae. hensilii*, *Ae. polynesiensis*, *Ae. africanus*, *Ae.camptorhynchus*, *Ae. luteocephalus,* and *Ae. notoscriptus*, among others. Around 27 species of mosquitoes have been identified as infected (naturally or experimentally), and only eight have been described as competent to transmit the virus (Table 1). A large number of these mosquitoes are considered vectors of other similar viruses such as DENV, CHIK, JENV, and WNV. Recent studies have proposed that *Culex quinquefasciatus* could be a new potential vector for ZIKV, based on the isolation of the virus in individuals from Colombia, Brazil, and China. However, there are contradictory outcomes from other studies which have shown that *Culex* mosquitoes cannot support virus replication and transmission. *Culex quinquefasciatus* is much more abundant than *Ae. aegypti* in several zones of the world; it has nocturnal foraging habits and a mostly subtropical geographic distribution. These could be important factors in vector control if this mosquito is proven to be a competent ZIKV vector.

Another important issue is related to the biological cycle of ZIKV; in sylvatic zones the cycle includes primates as main hosts and mosquitoes as vectors, while in residential zones the main host is humans. In residential zones the mosquito species implicated in the infection process are mainly *Ae. aegypti* and *Ae. albopictus*, both considered highly synanthropic, while in sylvatic zones other mosquito species are implied. The occurrence and density of these mosquitoes are related mainly to environmental suitability (high temperature and humidity) and the availability of resources for nesting, resting, and feeding such as stagnant water (essential to larval stages and oviposition) and poor sanitation conditions (hindering the elimination of individuals), among others (Fig. 3).

Perinatal Transmission

This pathway is the transmission from mother to child, mainly through the placenta. If the mother is bitten during pregnancy there is a significant probability of transmission to the fetus, generating potential congenital and neurological effects in the child. The probability of developing neurological abnormalities in fetuses increases if maternal infection occurs during the first trimester of pregnancy. There is also evidence of transmission during delivery of the newborn, due to the potential exchange of fluids associated with the presence of virus in the amniotic fluid, urine, and blood. Most recently, evidence shows possible transmission during breastfeeding of the newborn, identifying the presence of virus in breast milk, with a suspected case in Venezuela in 2017. Perinatal

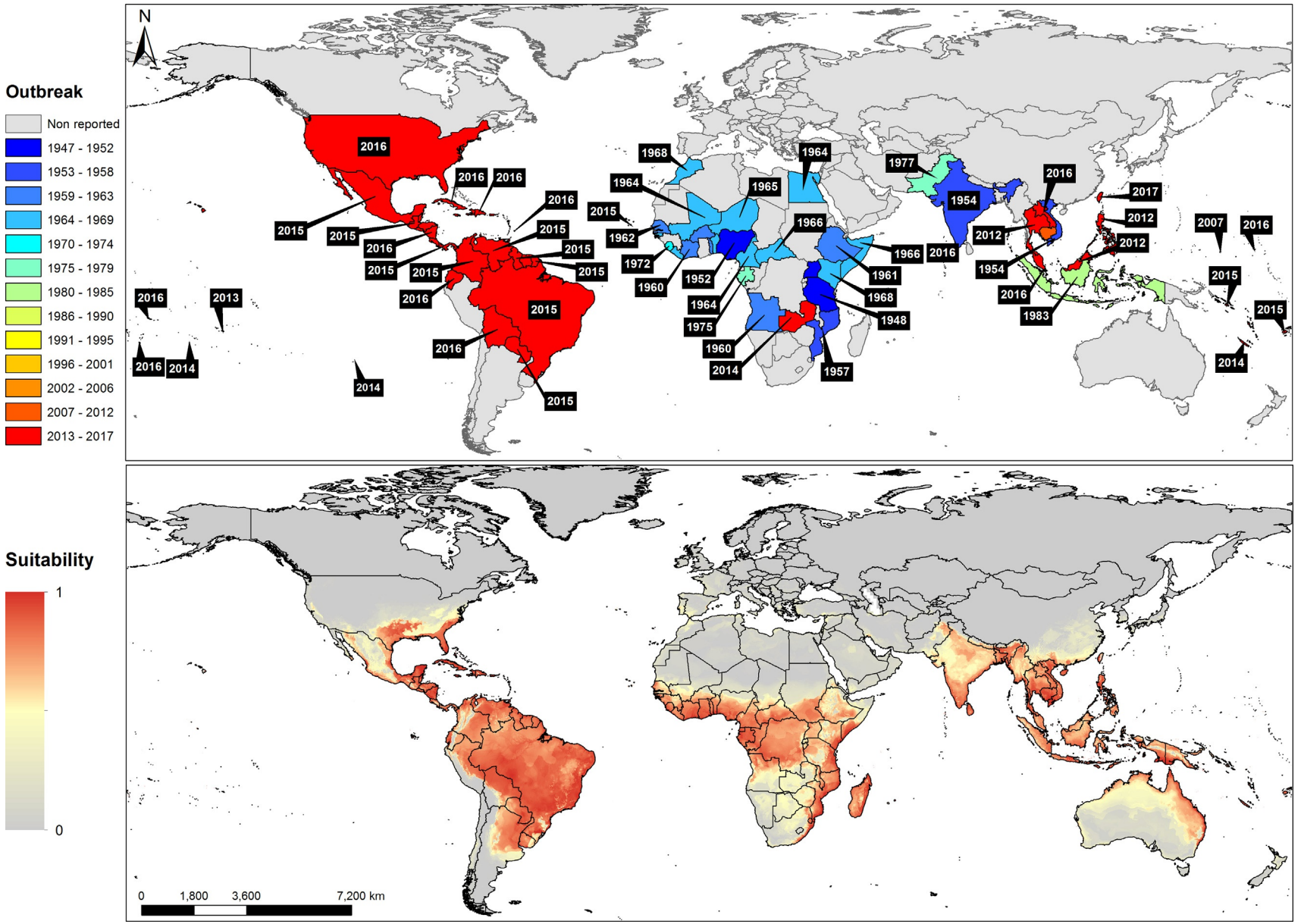

Fig. 1 (A) Map of the recorded ZIKV outbreaks worldwide (the *black labels* show the year of the first reported outbreak by country. (B) Environmental suitability model of *Aedes aegypti* worldwide [suitability is ranked from 0 (less suitable) to 1 (highly suitable)].

Fig. 2 Photography of an *Aedes aegypti* individual.

Table 1 Identification of ZIKV suggested vectors

Vector species	*Competent*	*Infected*	*Distribution*
Culicidae: Culicinae: Aedini			
Aedes aegypti	***	***	Worldwide
Aedes albopictus	***	***	Worldwide
Aedes africanus		***	Africa
Aedes apicoargenteus		*	Africa
Aedes camptorhynchus	*		Oceania
Aedes dalzieli		**	Africa
Aedes fowleri		**	Africa
Aedes furcifer		**	Africa
Aedes hirsutus		*	Africa
Aedes luteocephalus	*	**	Africa
Aedes metallicus		*	Africa
Aedes minutus		*	Africa
Aedes neoafricanus		*	Africa
Aedes notoscriptus	*		Oceania
Aedes opok		*	Africa
Aedes polynesiensis		*	Oceania
Aedes procax			Africa
Aedes taylori		**	Africa
Aedes unilineatus		*	Asia-Africa
Aedes vexans	**	*	Worldwide
Aedes vittatus	*	**	Africa-Asia
Aedes tarsalis		*	Africa
Culicidae: Anophelinae			
Anopheles coustani		*	Africa
Anopheles gambiae		*	Africa
Culicidae: Culicinae: Culicini			
Culex perfuscus		*	Africa
Culex quinquefasciatus	**	**	Worldwide
Culicidae: Culicinae: Mansoniini			
Mansonia uniformis		*	Oceania—Asia-Africa

*, competence and/or infection supported by a few studies or with a high number of studies with contradictory results; **, competence and/or infection supported by many studies but with other studies with contradictory results; and ***, competence and/or Infection highly probable with no contradictory results or a few studies with contradictory results.

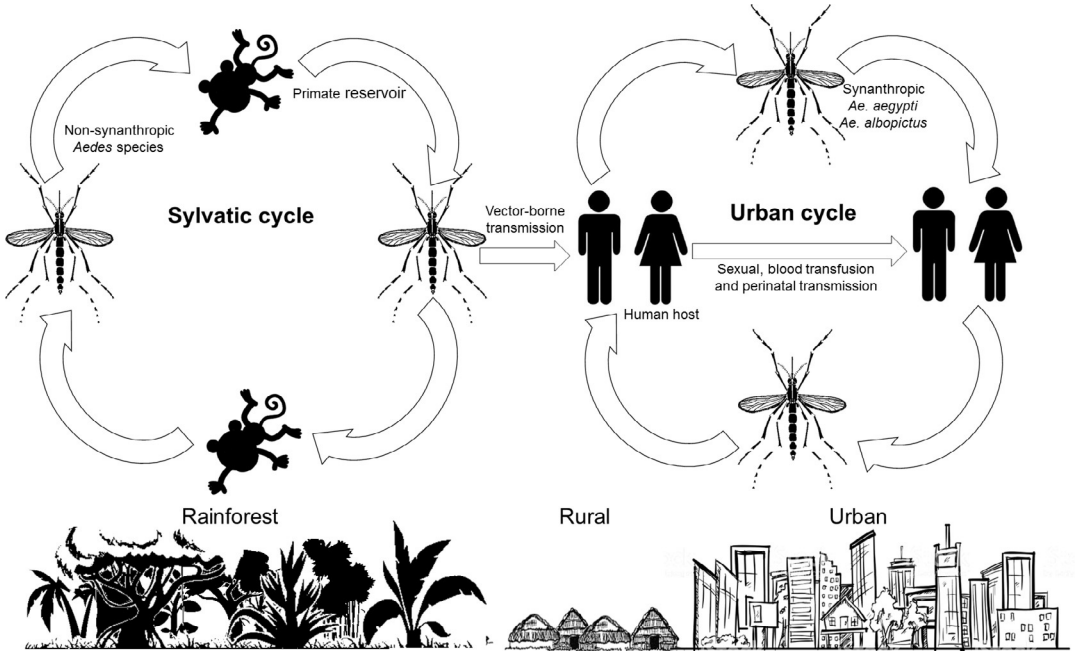

Fig. 3 Simplified scheme of the biological cycle of ZIKV highlighting the sylvatic (left) and urban (right) infection cycles. The scheme shows the habitat, reservoir, host, and main infection pathways of to each specific cycle.

transmission may be higher in territories with high abundance of mosquitoes, low natality control and poor quality of health services in the delivery process, which could lead to higher seroprevalence of ZIKV infection in children.

Sexual Transmission

The isolation of ZIKV viral particles in serum, blood, urine, semen, and vaginal fluid suggest the probability of transmission through sexual intercourse; confirmed cases have been detected worldwide. This type of transmission may occur from male to female, female to male, and male to male, considering vaginal and anal sexual intercourse. The presence of viral particles has been detected in semen until 60–70 days after the onset of signs and symptoms, while in vaginal mucosa the particles were detected until 21 days after the onset of signs and symptoms. The detection of this type of infection is difficult in endemic areas with predominance of vector-borne transmission, mainly due to high probability of infection by mosquitoes. Hence most detected cases are associated with imported infection by travelers from endemic to non-endemic areas. Prevention is based mainly on the use of condoms to avoid the probability of contagion, during the following months after travel to a zone with active transmission.

Blood Transfusion

This type of transmission pathway is related to the donation of blood from an asymptomatic patient in a blood bank or via transplant. The donation of blood from viremic patients could represent a new source of potential infection, representing a new threat, mainly in countries without protocols to detect the presence of viral particles in blood donations. This protocol consists of identification of a nucleic acid from the RNA-based viral particle which allows detecting seropositivity in asymptomatic donors infected with ZIKV. Studies have explored the possibility of inactivating ZIKV through the use of different methods similar to those used for DENV, CHIK, and WNV, however the recommendation is to prevent blood transfusion from seropositive ZIKV donors to patients.

Other Potential Transmission Pathways

Studies have described other potential transmission pathways based on evidence for similar viruses such as DENV, CHIK, WNV, among others. Nosocomial transmission associated with intrahospital pathogen transmission has been described for DENV, while zoonotic infection has been described from an infected animal reservoir to humans. Another potential pathway is related to the direct exchange of fluids from human to human, based on the presence of viral RNA viral particles in saliva until 5 days after the onset of signs and symptoms. This pathway has not been yet confirmed for ZIKV, but could represent a potential way of infection with the virus.

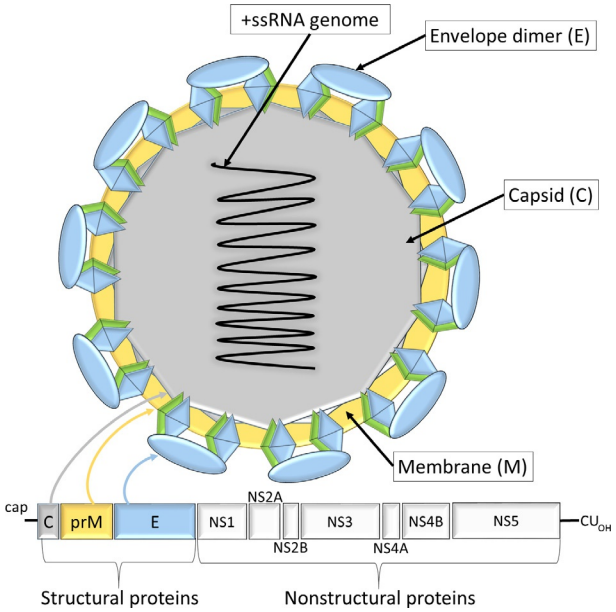

Fig. 4 Illustration of the structure of ZIKV. The upper part is a representation of the virus, while the lower part (*in boxes*) shows the proteins encoded by the viral genome.

Microbiology of the Virus

ZIKV is an icosahedron enveloped virus with a genome based on a positive-sense single-stranded ARN (+ssRNA; Virus type IV) with 10.7 kb length. The structure of the virus is based on three proteins, capsid (C), pre membrane (prM), and envelope (E). The virus genome leads to the codification of seven nonstructural proteins, which are involved in specific processes associated with the transcription and replication of the viral genome (NS proteins) (Fig. 4). The virion size ranges between 40 and 43 nm in diameter; it has a central core which contains the RNA and a lipid bilayer derived from the host cell which encloses the nucleocapsid. The replication of Zika occurs mainly in neural cells, however it has been reported that ZIKV may replicate within skin cells and immature dendritic cells. Replication occurs in both mosquito and mammalian cells. The virion replication cycle is highly dependent on pH; the optimum is a neutral pH of 6.8–7.4.

When the virion enters the host bloodstream after a mosquito bite, the viral particles penetrate the cell using different adhesion factors that generate attachment and entry. Then the membrane is dissolved within the host cell, delivering the RNA genome to the cell endosome; this process is highly sensitive to the pH characteristics of the host cell. The viral RNA in the cytoplasm is synthetized into the negative sense and then inserted in mRNA, directing the synthesis of positive viral RNA and membranes in the endoplasmic reticulum (ER) of the infected cell. The virion is assembled and buds within ER, moving through the Golgi complex. Finally, the prM is cleaved and the mature virion emerges from the *trans* Golgi network and is released by exocytosis. As a result, the cell lifecycle induces autophagy and interferon signaling in the infected cell, leading to the cell lysis.

Clinical Presentation

After infection the virus viremia ranges until 4–10 days after infection; activation of IgM and IgG antibodies occurs around 9 and 10 days after infection, respectively. Symptoms occur around 6 days after infection, and may persist for 1 or 2 more weeks. Zika virus generates mainly asymptomatic clinical presentation (around 80% of the cases); clinical complications are presented only in 20% of the infected patients. However, other studies have reported rates of around 40% of individuals with clinical symptoms. The most usual symptoms are maculopapular pruritic rash, low-grade fever, arthralgia, nonpurulent conjunctivitis, myalgia retro-orbital pain, fatigue, and headache. Unusual symptoms include vomiting, nausea, abdominal pain, diarrhea, and mucus membrane ulcers. Finally, some rare symptoms are facial edema, palatal petechiae, uveitis, desquamation of palms, severe pruritis, and gastrointestinal or respiratory complications (Fig. 5).

Complications of ZIKV

The infection of certain patients with ZIKV may generate serious complications, which are associated with congenital abnormalities and neurological conditions.

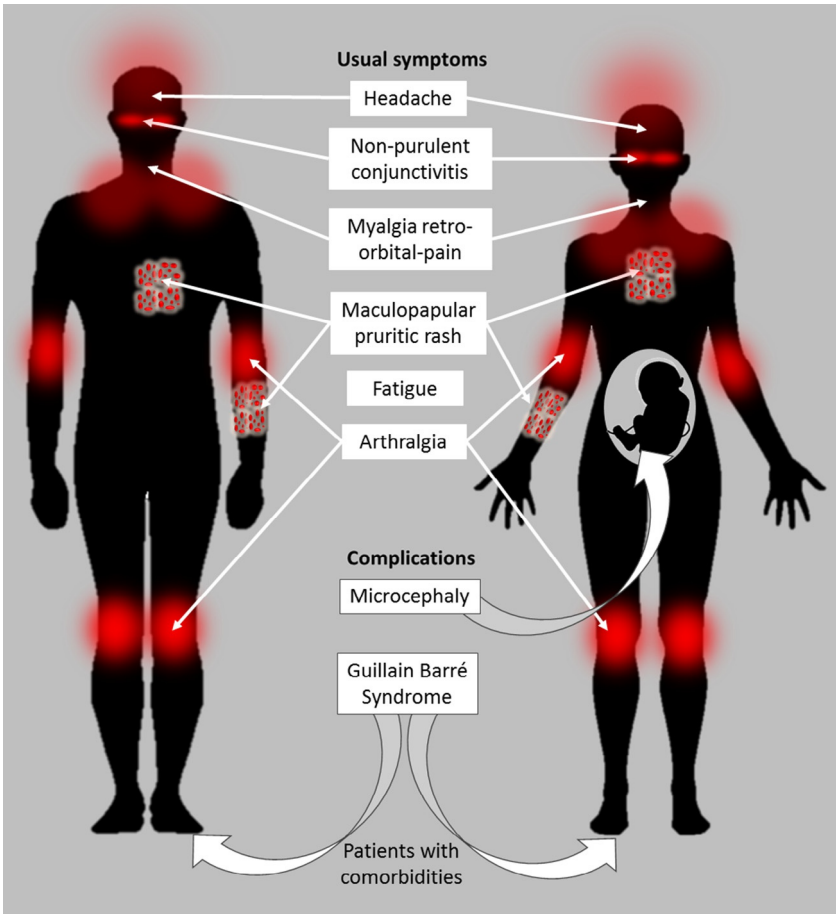

Fig. 5 Scheme of the usual symptoms associated with ZIKV infection in adult patients. The scheme also shows the two main complications derived from ZIKV infection in particular cases.

Guillain Barré Syndrome

An association between ZIKV and Guillain Barré Syndrome (GBS) has been proposed, due to the high increase in the number of reports of this condition after the ZIKV outbreaks during the last 10 years. GBS is a serious neurological condition associated with a dysfunction in which the nervous system is attacked by the immunological system. This autoimmune disorder affects the myelin of the nerves, which decreases the quality and velocity of nervous signals and can even cause paralysis or death by weakening of the respiratory muscles. Other effects of GBS are dysfunction of tendon reflexes and even cranial nerve disorders.

During the outbreak in French Polynesia in 2013, 74 cases were identified with neurological symptoms; 42 cases were diagnosed with GBS. In the outbreak in Brazil in 2015, 121 cases of neurological symptoms were identified in Bahia state, 49 of which were diagnosed with GBS, all with ZIKV symptoms such as rash. In Colombia from 327 cases with neurological symptoms 227 were diagnosed with GBS, all had presented ZIKV symptoms.

Studies have proposed that the GBS incubation period ranges between 2 and 23 days after the presentation of ZIKV symptoms. The risk group to GBS illness due to ZIKV is limited to patients with comorbidities (presence of previous conditions) such as immunosuppressed or chronic patients. A very low death rate from GBS due to ZIKV has been reported, with only two reported cases.

Microcephaly

The relation of ZIKV and microcephaly was initially suggested by an epidemiological approach based on the increase in the amount of microcephaly cases in Brazil during the outbreak of 2015–16 (around 20 times the usual number of cases). This hypothesis was reinforced by the identification of ZIKV antigens in amniotic fluids and neural cells of fetuses of spontaneous abortions. Currently the relation between microcephaly and ZIKV infection through transplacental pathway has been widely proven, supported by experimental studies on animals and analysis of infected humans.

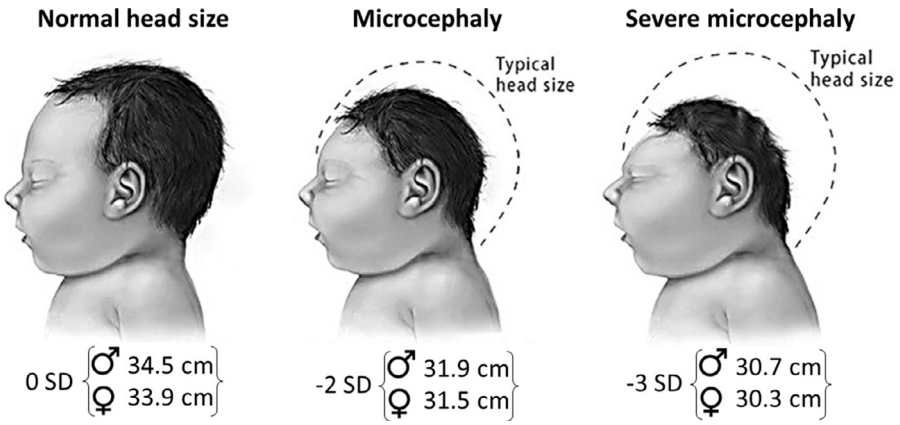

Fig. 6 Comparative scheme of head size according to the presence and level of microcephaly associated with ZIKV infection. The bottom panels show the circumference of head by sex according to the level of microcephaly (SD means standard deviation). Original photography by CDC.

Microcephaly is a congenital clinical condition related to small head size of the newborn, with an occipitofrontal head circumference more than 2 SD below the median (compared to a healthy child). The clinical condition of microcephaly does not always generate problems of brain development. The level of potential brain abnormality is related to the severity of microcephaly, being considered a severe clinical presentation 3 SDs below the median size of a healthy child. There are two types of microcephaly, depending mainly on the gestational period of development; primary microcephaly, which is generated before 32 weeks, and secondary microcephaly which is developed after that threshold (Fig. 6). The first type is related to failures in neurogenesis (generation of neuronal cells) and death of neuronal progenitors, while the second is associated with postnatal problems of cell maturation. Studies have identified that the main cause of microcephaly associated with infection is related to the perturbation of neural progenitor population by the pathogen. Zika virus infects neural progenitors, inducing a reduction of neuron production and the ventricular zone, and generating small organoids. This arrests the normal cell cycle and induces cell death, generating a deficit of neuron cell production and hence decreasing the growth of cerebral mass.

Cases of microcephaly associated with ZIKV have been reported in 31 countries. An incidence of around 5.4% of the women of childbearing age (5400 in 100,000) was reported in Brazil. Additionally, in the same outbreak congenital anomalies were identified in 5% of the infants exposed to ZIKV during pregnancy; microcephaly was identified in 75% of these cases. Currently public health strategies for microcephaly control associated with ZIKV are focused on prevention, mainly through natality control during infection periods, and by recommending that pregnant women avoid traveling to active transmission zones during these periods.

Other Congenital Complications

The Zika virus also generates other brain anomalies such as ventriculomegaly, brain calcification, cerebellar hypoplasia, cortical and subcortical corpus callosum hypoplasia, craniofacial disorder, hearing loss, delayed myelination, and enlarged cisterna magna. In infants with microcephaly the two most common detected brain anomalies were brain calcification and ventriculomegaly, which were present in 99% and 94% of the cases, respectively.

Ocular pathologies associated with ZIKV have been reported (mainly associated with cases of infants with microcephaly) such as macular atrophy, pigment mottling, optic nerve anomalies, lacunar maculopathy, foveal reflex loss, congenital glaucoma, epiphora, blepharospasm, corneal clouding, photophobia, buphthalmos, and increased intraocular pressure. Studies have reported an incidence of ocular anomalies of 34%–38% of the cases of infants with microcephaly due to ZIKV in the Brazil outbreak; pigment mottling and optic nerve anomalies were the two most common ocular problems with 64.7% and 47.1% incidence, respectively. Also ocular complications have been reported in adult patients, but the incidence of ocular pathologies in patients without microcephaly remains unclear.

Evidence indicates that ZIKV can induce cardiac anomalies such as ostium secundum atrial septal defect, small apical ventricular septal defect, and large ventricular septal defect. The incidence of these types of pathologies is around 13% in patients with microcephaly. Other congenital complications described are musculoskeletal abnormalities such as unilateral/bilateral clubfoot and congenital arthrogryposis multiplex; both correspond to contractures of extremities which present an abnormal position. The conjunction of the abovementioned pathologies and anomalies led to the name "Congenital Zika virus Syndrome" (CZS), which entails serious sequels in children infected during pregnancy, mainly associated with mental retardation, motor disabilities, and visual/auditory deficiencies.

Diagnosis

The detection of ZIKV is based on two main approaches, serological tests and nucleotide acid amplification tests. Serological tests are based mainly on the increase of the specific antibodies IgM and IgG, which respond to flaviviridae viruses. A serological test can

be applied to serum and cerebrospinal fluids. It has been suggested that diagnosis using serum may not be reliable if the patient has been previously infected with DENV, YFV of CHIV, because they can cross-react due to high similarity between them. The infection induces plaque reduction, which can be useful to ensure the diagnosis if the other serological tests are not sufficiently conclusive. The serological tests are applied through an ELISA/EIA test as a screening; because they do not provide conclusive results it is always recommended to apply another test to obtain a final result. This type of test is recommended from 4 days up to 12 weeks after the onset of symptoms.

The other pathway to generate a ZIKV diagnosis is viral nucleic acid detection in fluids through molecular methods like real time PCR (RT-PCR). The most commonly used samples are urine and blood; other samples such as breast milk, saliva, amniotic fluid, cerebrospinal fluid, and semen may produce positive results, but they are less used in diagnosis. The test aims to detect specific genes of ZIKV present in fluids; the targets of detection are the Pre membrane (prM), Envelope (E), or NS5 encoding genes. The reliability of the results depends on the time period in which it is applied because ZIKV does not remain for the same length of time in all the samples, for example, ZIKV remains longer in urine than in blood, hence it can be a better sample if the test is applied belatedly after symptom onset. Additionally, urine samples have been proven to have a higher load of viral RNA than blood, while saliva also has a higher viral RNA load than blood but with a shorter time period. Studies recommend applying RT-PCR on both blood and saliva, and depending on the time since infection and symptom onset, on urine (especially in late stages of infection until 12 weeks).

Treatment

The current state of treatment against ZIKV is focused on supportive care associated with the infection symptoms, while an effective vaccine remains under development. Nonsevere symptomatic clinical presentation of ZIKV mainly generates a mild disease, in which case bed rest, drinking fluids and fever/pain therapy with medicines (e.g., analgesic and antipyretic) are recommended. If the symptoms become severe hospitalization of the patient is recommended. Currently drug development is focused on two main therapies, interferons (IFN) and nucleoside analogs. The IFN have good performance against other viruses such as DENV and WNV; IFN has been experimentally shown to hinder viral replication in early stages by altering plasma membrane properties. IFN also causes an impairment in viral replication and translation associated with the polyamine depletion induced by the catabolic enzyme spermine/spermidine N1-acetyltransferase (SAT1). The enzyme cholesterol-25-hydroxylase (CH25H), another IFN, acts by hindering viral fusion with the host membrane, thus inhibiting the entry of the virion to the cell. Nucleoside analogs act mainly on viral proteins, generating their premature termination. Studies suggest that *C*-methylated nucleosides can be used against ZIKV, showing a moderate anti-ZIKV effect in murine models. The effect of nucleoside analogs is focused on generating premature termination of RNA synthesis, viral receptor and entry to the host cell. Treatment with nucleoside analogs has proven to generate negligible toxic effects, while IFN generate more severe side effects; medication during pregnancy with both treatment types is dangerous due to the side effects. The main challenge of drug development against ZIKV is to consider a broad spectrum of activity (multitarget approach) aiming to deal with possible mutation or evolution of the virus.

Prevention

The prevention strategies of ZIKV currently are mainly associated with controlling the vector, reducing the suitable environmental/habitat conditions of the mosquito and reducing human exposure to the vector. There are some main risk groups to this virus, which are mainly pregnant women (specifically the fetuses) and patients with comorbidities, because both have significant probabilities of developing serious chronic and neurological sequels if they become infected (microcephaly and GBS). Prevention strategies against ZIKV should be focused on reducing the potential exposition to the virus, implementing for example, the use of mosquito repellent, use of condoms to avoid sexual transmission, using more covered clothes in sylvatic zones and avoiding travel to zones with high abundance of the *Aedes* mosquito, among others. Outside the endemic areas of the virus it is recommended to avoid travel to zones with active transmission if you belong to a risk group. If a person traveled to an endemic area and is suspect to be infected, it is recommended to avoid blood donation and use prophylactics in sexual intercourse. In endemic areas it is recommended to manage the home environment, aiming to avoid the generation of potential habitats and resources to mosquitoes by avoiding stagnant water, closing doors and windows, and applying insecticides against mosquitoes.

The vaccination of risk groups and the general population is one of the main strategies used against many viruses worldwide, however, there is not yet available a reliable therapy or vaccine for ZIKV. Currently different labs and institutions are working on the development of an effective vaccine against ZIKV (around 18 companies) since the outbreak in America in 2015. There are six main types of vaccines under development; purified inactivated vaccine (PIV), DNA-based platform, mRNA, subunit vaccines, viral vector vaccine, and virus-like particles (VLP). Some vaccines under development are focused on specific viral proteins such as prM and E, while others are focused on the whole virion by releasing purified inactivated or attenuated copies of the virus to induce the immunogenic response. Studies support that the most effective vaccine may be the vector-based vaccine, because this method has proven to produce high immunogenicity against other similar viruses such as DENV, YFV, and JEV. The challenges to vaccine development are to deal with cross reactivity with other similar viruses, ensure high immunogenicity, sustain a prolonged protection in humans and avoid secondary effects. Since the Brazil outbreak there is great progress in this matter.

Control

As for other mosquito-borne infectious diseases, control actions are based mainly on mosquito eradication, which can be done using biological, mechanical, or chemical agents.

Biological Control

- Bacteria: *Aedes* mosquitoes are susceptible to the bacterium *Wolbachia*, which acts as biological control agent by reducing the lifespan of females. Additionally, this bacterium generates a cytoplasmic incompatibility which leads to a reduction in ZIKV competence. *Wolbachia* is transmitted from females to larvae, reducing their competence to replicate and carry ZIKV. This method has proven be effective, reducing significantly the transmission of ZIKV.
- Fungi: biological control agents such as *Metarhizium anisopliae* and *Beauweria bassiana* also have proven to be effective against the *Aedes* mosquito; these fungi infect the organs of the mosquito, inducing its death. Another advantage of this type of fungi is their wide dispersal capacity through spores, which make them highly effective in insect population control.
- Predatory mosquitoes: Another strategy is the use of non-hematophagous predator mosquitoes such as *Mesocyclops aspericornis* and *Toxorhynchites speciosus*, which prey on *Aedes* mosquitoes, controlling their population.
- Copepods: *Mesocyclops* and *Macrocyclops* are able to control *Aedes* larvae during first and second instars. These organisms were used to control DENV in Vietnam in year 2002–2003. These organisms affect the anal segment, the siphon and the abdomen of larvae, increasing their mortality.
- Plants: Some plants have the capacity to synthesize natural substances which have high toxicity to mosquitoes in different life stages. Herbal extracts are an eco-friendly option against *Aedes*, because the toxicity to other species is usually low, however it is necessary test their toxicity to the other species of the ecological assemblage before their application.
- Fish: Species such as *Gambusia affinis*, *Gambusia holbrooki*, *Poecilia reticulata*, among others have been widely used as biological control agents against mosquitoes, showing very good performance in larva control. Nevertheless, among the adverse effects of this kind of species is the decline of local fish and insect fauna, because these species are highly likely to become invasive, generating serious ecological effects.
- Tadpoles: Different species of frogs may be effective predators of *Aedes* larvae during the tadpole stage, especially *Bufo*, *Euphlyctis*, *Hoplobatrachus*, *Polypedates*, and *Ramanella*. However, the role of these organisms as mosquito biological controllers remains under study.

Chemical Control

Different chemical substances have been used to control mosquito species worldwide; their effects may be focused on larvae or the adult stage of the insect. The most used products include pyrethroids, organochloride, and organophosphorus, which attack the nervous system of the insect. This type of control mechanism could induce the resistance of mosquitoes through adaptation to the chemical compounds, hence the prolonged application of these products is not recommended. Additionally, chemical control cannot differentiate between target and nontarget insects, hence their application affects significantly other species of the ecosystem.

Mechanical Control

This type of control is related to the removal of potential sites of mosquito nesting such as old tires or empty planters. This type of control can be applied by each family to avoid the possible proliferation of *Aedes* mosquitoes in domiciliary areas.

Genetic Tailoring

This type of control aims to modify the genome of mosquitoes by introducing a lethal gene which can be transmitted, inhibiting tetracycline synthesis. The genetically modified mosquitoes are introduced into the environment where reproduction with the nonmodified mosquitoes generates larvae with the failed gene, which are incapable of surviving.

Sterile Mosquitoes

This strategy has been used to control a large number of species with epidemiological or economic importance such as vector mosquito species and the Mediterranean fruit fly. The insects are exposed to radioactivity which induces their sterilization, making them unable to reproduce. Then these sterile insects are released in the environment, reducing the reproductive success of the population. Another way of insect sterilization is by genetic modification of the RNA of male mosquitoes; this kind of sterilization is less invasive since it does not use radiation which can be harmful.

Future Perspectives of ZIKV

Studies have identified an estimated 2.2 billion people under risk associated with exposure to the main vector, this number can be significantly affected by different social and governmental conditions of each territory. Currently the incidence of infectious diseases is highly influenced by many factors which can induce the proliferation of disease, such as climate change, land use change, pollution, poverty, public health, and others.

The global environmental degradation associated with human influence is an undeniable truth, climate change being the most significant effect generated by human activities. Climate change has generated a global average increase of 1°C, while precipitation regimes have experienced significant modifications across the globe. In some territories there is an increase of the amount and intensity of rain such as the monsoon affected countries, while other zones of the world there is a large decrease in precipitation, such as Mediterranean and temperate areas. Climate regimes have become more unpredictable; this modifies the environmental conditions for the development of diseases, contributing to the occurrence of more frequent and unpredictable epidemiological outbreaks and shifting the geographic range of mosquitoes, leading to the possible colonization of new areas. Climatic phenomena such as hurricanes, droughts, floods, and storms will become more frequent and intense, hence their effects can also modify the vulnerability of human populations, increasing their receptivity to infectious diseases due to a degradation of life quality conditions. It is necessary to develop new strategies to predict potential epidemiological outbreaks or shifts of geographic ranges of vectors, aiming to prevent the infection of people, hence the generation of spatially explicit models to identify vulnerable areas and new areas potentially affected is recommended.

The influence of land use and cover change represents the main driver of species extinctions, which generates the depression of species diversity and exposes the human population to new zones which were sylvatic before. Studies have identified the role of species diversity in reducing the proliferation of reservoirs and the success of invasive species. More diverse ecological assemblages usually generate a biotic resistance to the introduction and success of invasive species, mainly because if the community is more diverse there is a high probability to find predators and competitors of the invasive species. More diverse ecological communities also generate a dissolution effect, because the probability of encounter between competent reservoirs, vectors and hosts is reduced due to the presence of a high number of incompetent species. Thus it is necessary to generate a sustainable land use policy, aiming to prevent the deforestation of rainforests and to reduce the exposure of new populations. Additionally, it is necessary to improve the management of urban and rural zones, aiming to reduce the availability of nesting sites, improve the life quality of the population and avoid exposing more population due to unregulated urban growth.

The reduction of population vulnerability and exposure is a big challenge for public health; the strategies should point to the education of the population, focusing on the most vulnerable groups. Educational campaigns can reduce the susceptibility of the population by recommending the use of contraceptive methods to avoid sexual and perinatal transmission, improving home environmental conditions by applying insecticides, reducing the potential nesting sites, and maintaining houses and neighborhoods clean. Then the policies should focus on improving public health coverage and quality, aiming to deal with potential epidemiological outbreaks, improving the diagnosis, and treatment of the suspected cases, which can reduce the dispersion of the virus though other transmission pathways such as sexual transmission or blood transfusion. Until the development of a reliable vaccine to deal with ZIKV, the management of environmental conditions and populations of vectors and the reduction of host susceptibility are the main focus. When the vaccine is ready the governments need to ensure the access to the population, especially to the most vulnerable groups.

Further Reading

Alam A, Imam N, farooqui A, Ali S, Malik MZ, and Ishrat R (2017) Recent trends in ZIKV research: A step away from cure. *Biomedicine & Pharmacotherapy* 91: 1152–1159.

Alaniz AJ, Bacigalupo A, and Cattan PE (2017) Spatial quantification of the world population potentially exposed to Zika virus. *International Journal of Epidemiology* 46: 966–975.

Ali S, Gugliemini O, Harber S, Harrison A, Houle L, Ivory J, Kersten S, Khan R, Kim J, Leboa C, Nez-whitfield E, Marr JO, Rothenberg E, Segnitz RM, Sila S, Verwillow A, Vogt M, Yang A, and Mordecai EA (2017) Environmental and social change drive the explosive emergence of Zika virus in the Americas. *PLoS Neglected Tropical Diseases* 11: e0005135.

Asif A, Manzoor S, Tuz-Zahra F, Saalim M, Ashraf M, Ishtiyaq J, and Khalid M (2017) Zika virus: Immune evasion mechanisms, currently available therapeutic regimens, and vaccines. *Viral Immunology* 30(10): 682–690.

Basile K, Kok J, and Dwyer DE (2018) Zika virus: What, where from and where to? *Pathology* 49: 698–706.

Baud D, Gubler DJ, Schaub B, Lanteri MC, and Musso D (2017) An update on Zika virus infection. *Lancet* 390: 2099–2109.

Bernardi De A, Malone RW, Guo J-T, Homan J, Linchangco G, Witter ZL, Vinesett D, Damodaran L, and Janies DA (2016) Molecular evolution of Zika virus as it crossed the Pacific to the Americas. *Cladistics* 33: 1–20.

Epelboin Y, Talaga S, and Dusfour I (2017) Zika virus: An updated review of competent or naturally infected mosquitoes. *PLoS Neglected Tropical Diseases* 11: e0005933.

Javed F, Manzoor KN, Ali M, Haq IU, Khan AA, Zaib A, and Manzoor S (2018) Zika virus: What we need to know? *Journal of Basic Microbiology* 58: 3–16.

Lessler J, Chaisson LH, Kucirka LM, Bi Q, Grantz K, Salje H, Carcelen AC, Ott CT, Sheffield JS, Ferguson NM, Cummings DA, Metcalf CJ, and Rodriguez-Barraquer I (2016) Assessing the global threat from Zika virus. *Science* 353: aafs160.

Mittal R, Nguyen D, Debs LH, Patel AP, and Liu G (2017) Zika virus: An emerging global health threat. *Frontiers in Cellular and Infection Microbiology* 7: 486.

Musso D and Gubler DJ (2016) Zika virus. *Clinical Microbiology Reviews* 29: 487–524.

Passi D, Sharma S, Dutta SR, and Ahmed M (2017) Zika virus diseases—The new face of an ancient enemy as global public health emergency (2016): Brief review and recent updates. *International Journal of Preventive Medicine* 2017(8): 6.

Petersen LR, Jamieson DJ, Powers AM, and Honein MA (2016) Zika virus. *The New England Journal of Medicine* 374: 1552–1563.

Saiz J, Vázquez-Calvo Á, Blázquez AB, Merino-Ramos T, Escribano-Romero E, and Martín-Acebes MA (2016) Zika virus: The latest newcomer. *Frontiers in Microbiology* 7: 495.

Singh RK, Dhama K, Khandia R, and Munjal A (2018) Prevention and control strategies to counter Zika virus, a special focus on intervention approaches against vector mosquitoes—Current updates. *Frontiers in Microbiology* 9: 87.

Song B, Yun S, Woolley M, and Lee Y (2017) Zika virus: History, epidemiology, transmission, and clinical presentation. *Journal of Neuroimmunology* 308: 50–64.