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ZIKA VIRUS: A CHALLENGE FOR HUMANS

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ABSTRACT: Zika virus infection is caused by the bite of an infected Aedes mosquito, usually causing rash, mild fever, conjunctivitis, and muscle pain. First time the virus was isolated in 1947 in the Zika forest in Uganda. It is transmitted to people through the bite of an infected Aedes mosquito. Symptoms are similar to those of dengue and chikungunya, which are transmitted by the same type of mosquito. Autoimmune and Neurological complications are infrequent. Treatment consists of relieving pain, fever, and any other symptom that inconveniences the patient. To prevent dehydration, it is recommended to drink plenty of water, rest, and control the fever. Thus far, there is no vaccine for the virus. But since it is a self-remitting disease, a person can be hopeful of being cured within a week or two, and the treatment is usually symptomatic. This review covers about the Zika virus; epidemiology and guidelines issued by the health ministry for control and prevention of Zika infections.

INTRODUCTION: Zika virus (ZIKV) is an arthropod-born virus (arbovirus) belonging to the genus Flavivirus and the family Flaviviridae [1]. The virus carries the name of the forest where it was first identified [2], a name that means "overgrown" in the Luganda language [3, 4]. This single stranded RNA virus is close to the Spondweni virus, identified in South Africa. Genomic comparisons have revealed various sub lades indicating two major lineages, Asian and African. The diagnosis of ZIKV infection relies mostly on the detection of viral RNA in blood samples: RT-PCR and viral isolation in blood samples collected less than five days after the onset of symptoms are the reference techniques.

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The "pan flavivirus" amplification technique combined with sequencing may be used as an alternative [5, 6]. The viremic period in humans could be short, from the third to the fifth day after onset of symptoms. Viruria could last longer than viremia and the RT-PCR detection of viral RNA in urine could be an alternative method if genetic material is no longer present in the serum [7, 8, 9].

Serological tests (Elisa or immune fluorescence) are also widely used. The centers for disease prevention and control (CDC) in Atlanta had developed an ELISA technique to detect specific anti-Zika IgM during the epidemic in Yap, in 2007 [10]. The frequency of cross-reactions with other flaviviruses (dengue, yellow fever) may make the diagnosis difficult. Furthermore, in the early phase of infection, the rate of IgM and IgG may be very low, making it difficult to confirm the diagnosis. The detection of antibodies should be confirmed by a complementary seroneutralization assay allowing determining the specificity of the detected

antibodies (*e.g.* Plaque Reduction Neutralization Test [PRNT]) and proving a 4-fold increase of the antibody titer initially found [8]. For the detection of antibodies specifically related to ZIKV no commercial kit is currently available. Scientists have worked out the structure of the Zika virus in a breakthrough that will aid the development of treatments to combat infection.

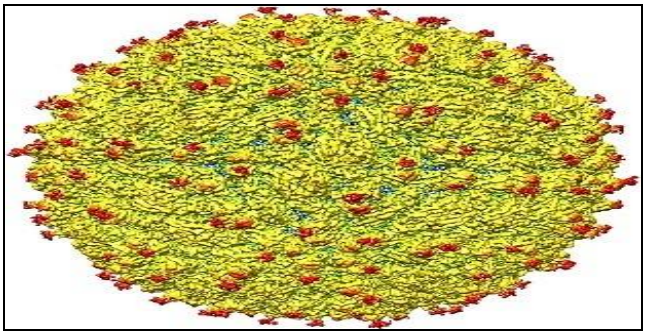

FIG. 1: ZIKA VIRUS STRUCTURE SIMILAR TO VIRUSES SUCH AS DENGUE AND WEST NILE

Epidemiology: The first isolate of ZIKV was obtained from the brain of mice inoculated with the serum of *Rhesus* 766 the monkey which had been placed in a cage in a tree platform as part of the yellow fever program of the Rockefeller foundation [11]. One year later, a second isolation of the virus was obtained from the mosquito *Aedes africanus* in the same forest [12]. Further serological studies confirmed that humans could be infected by ZIKV [13] and transmission of the virus by artificially fed *Aedes aegypti* mosquitoes to mice was reported [14]. Sporadic isolation of the virus from humans was obtained in studies in Nigeria in the next decades [15, 16] several studies in Africa (Uganda, Tanzania, Egypt, Central African Republic, Sierra Leone, and Gabon) and Asia (India, Malaysia, the Philippines, Thailand, Vietnam, and Indonesia) reported serological evidence of the spread and distribution of the virus [17].

TABLE 1: EPIDEMIOLOGICAL AND CLINICAL FEATURES OF DENGUE, ZIKA, AND CHIKUNGUNYA VIRUS INFECTIONS

	Dengue virus	Zika virus	Chikungunya virus
		Virology	
Family	Flaviviridae	Flaviviridae	Togaviridae
Nucleic acid	Single-strand, positive sense, RNA	Single-strand, positive sense, RNA	Single-strand, positive sense, RNA
Main divisions	4 serotypes (1 to 4)	2 lineages (African and Asian)	4 major lineages (West African, East/Central/South African [ECSA], Indian Ocean, Asian)
		Epidemiology	
Natural reservoir	Primates (sylvatic cycle)	Primates (sylvatic cycle)	Primates (sylvatic cycle)
Key vectors for natural transmission	*Aedes* mosquitoes. **Sylvatic cycle:** *A. furcifer, A. luteocephalus, A. vittatus, A. taylori, A. niveus.* **Urban cycle:** *A. aegypti and A. albopictus* other locally predominant species implicated (*e.g. A. polynesiensis, A. pseudoscutellaris, A. malayensis, A. cooki)*	*Aedes* mosquitoes. **Sylvatic cycle:** *A. africanus, A. furcifer, A. luteocephalus, A. vittatus, A. unilineatus, A. opok.* **Urban cycle:** *A. aegypti, A. albopictus;* other locally predominant species implicated (*e.g. A. hensilli, A. polynesiensis)*	*Aedes* mosquitoes. **Sylvatic cycle:** *A. africanus, A. furcifer, A. luteocephalus, A. neoafricanus, A. taylori, A. dalzieli, A. vigilax, A. camptorhynchites, A. fulgens.* Possibly *Mansonia spp*. as well. **Urban cycle:** *A. aegypti, A. albopictus*
Endemic areas	Tropics and subtropic areas. Widespread in Asia, Africa, Latin America, Pacific islands, Northeast Australia. Increasing cases reported in south-western and south-eastern United States	Asia: Cambodia, Indonesia, Malaysia, Pakistan, The Philippines, Thailand. Pacific islands: Micronesia, French Polynesia, New Caledonia, The Cook Islands. Africa: Senegal, Uganda, Nigeria, Coˆte d'Ivoire, Gabon, Tanzania, Egypt, Central African Republic, Sierra Leone. Latin America: since 2015.	Widespread in sub Saharan Africa, Asia, Latin America, Pacific islands, Indian Ocean island s.c Europe: local transmission in northern Italy (2007) and southern France (2014) following importation of the virus
Iatrogenic transmission	Transfusion-transmission confirmed; possibly renal transplantation	One case of transfusion transmitted infection declared by Brazilian authorities	Transfusion-transmission potentially possible
Vertical infections	Yes. No congenital	Yes. Possible association with	Yes. Possible centro-facial

	Abnormalities reported	microcephaly and maculopathy	hyperpigmentation
Sexual transmission	Not reported	Yes	Not reported
		Clinical features	
Incubation period	3-10 days (usually 5-7 days)	2-12 days (usually 2-7 days)	2-6 days
Duration of viraemia	2-3 days before to 4-5 days (range: 2-12 days) after onset of symptoms	Usually 3-5 days after onset of symptoms (possibly over 11 days in some cases). Duration of viraemia prior to disease onset unknown	About 6 days after onset of symptoms (range: 3-10) days
Asymptomatic infection	14% in adults, 53% in children. Over 75% in some series	80%	3-37%
Common clinical manifestations	Fever, headache, retro-orbital pain, maculopapular rash or "white islands in a sea of red", arthralgia, myalgia	Fever, headache, conjunctivitis, itchy maculopapular rash, arthralgia (small joints of hands and feet), oedema of extremities, oral ulcers	Fever, rash, myalgia, polyarthralgia, polyarthritis, diarrhoea, vomiting, abdominal pain
Uncommon or severe manifestations	Severe dengue: vascular leakage, Haemo concentration, bleeding diathesis, shock, end organ Involvement (previously referred to as dengue haemorrhagic fever and dengue shock syndrome)	Guillain-Barre´ syndrome, encephalitis, meningo encephalitis. Possible congenital infection leading to microcephaly and maculopathy	Conjunctivitis, uveitis, iridocyclitis, retinitis, meningo encephalitis, myocarditis, hepatitis, multi-organ failure
Case-fatality ratio	Less than 1% to 5% with dengue fever. Severe dengue without adequate treatment, up to 20% or above, but can be reduced to less than 1% with proper management	Very low	0.1%
Key laboratory findings	Leukopenia, lymphopenia, thrombocytopenia, elevated transaminases. Haemoconcentration (increased haematocrit) and coagulation abnormalities in severe dengue	Relatively normal blood tests. Occasional mild thrombocytopenia, leukopenia with monocytosis reported	Leukopenia, lymphopenia, thrombocytopenia, hypocalcaemia, elevated transaminases
Diagnostic tests of choice	NS1 antigen detection, RT-PCR, antibody detection	RT-PCR, antibody detection (ELISA and neutralization assay)	RT-PCR, antibody detection

[a] Updated map of countries with dengue transmission can be found at http://www.healthmap.org/dengue/en/.
[b] Updated map of American countries with autochthonous Zika virus transmission during the 2015 outbreak can be found at Regional Office for the Americas of the World Health Organization,http://www.paho.org/hq/index.php?optionZcom_content&viewZ article&idZ11669&ItemidZ41716&langZen.
[c] Updated map of countries with chikungunya transmission can be found at http://www.cdc.gov/chikungunya/geo/.
[d] Quoted by the Center for Infectious Disease Research and Policy, The University of Minnesota, on 4 February 2016. No official scientific publications are available at the time of writing. Available at: http://www.cidrap.umn.edu/news-perspective/2016/02/brazilconfirms- blood-transfusion-zika-paho-calls-global-support. [Accessed 18.02.16.]

Sporadic isolation of the virus was latterly reported from humans in Senegal and Central African Republic as well as from mosquitoes in Ivory Coast, Burkina Faso and Malaysia [18, 19]. In 2007 an outbreak in the Yap Islands of the Federated States of Micronesia (in the western Pacific Ocean, north to Papua New Guinea) [20, 21]. Initiated the spread of ZIKV among the Pacific region. In 2013 a major epidemic broke out in French Polynesia [22, 23] and first autochthonous cases were reported in New Caledonia [24] by the beginning of 2014 and later from the Cook Islands [25] Vanuatu and Solomon Islands. At the same time, in January 2014 a case of Zika fever was confirmed in the Eastern Island (Chile) with forty more cases suspected [26]. During 2014, imported cases from the Pacific region were reported in travelers in Norway, Germany, Australia, France, Canada, Italy and Japan [27, 28].

In May 2015 the first cases of the ZIKV epidemic in the continental Americas were reported when 17 cases of Zika fever were confirmed from three states in Brazil: Bahia (8 cases), Rio Grande do Norte (8 cases) and São Paulo (1 case). Since then, the virus has spread in an explosive pandemic through South and Central America and the Caribbean. From October 2015 to February 2016, autochthonous transmission of ZIKV has been

reported with more than 125.000 suspected cases in 28 countries [29]. Outside of the Americas, the Atlantic island nation of Cape Verde announced its first ZIKV epidemic in October 2015. First sequencing studies suggest that the pandemic is due to the Asian lineage as happened in the epidemic at the pacific region [30, 31].

TABLE 2: OUTBREAKS OF HUMAN ZIKA VIRUS INFECTION SINCE 2007 [32, 33]

Year	Location	Estimated number of cases	Notable features
2007	Yap Island, Micronesia	49 confirmed 59 probable, and 72 suspected cases in one study. Estimated over 900 clinical cases, 73% of population infected in 4 months.	*Aedes hensilli* implicated as the main vector
2007	Gabon	Detected in 5 archived human samples; total number of cases unknown	Retrospective study of a concurrent outbreak of dengue and chikungunya; detection of virus in patient sera and *A. albopictus* pools
2013-2014	French Polynesia	8,723 suspected cases, over 30,000 sought medical care	Derived from the Asian lineage, closely related to Cambodia 2010 and Yap state 2007 strains. Association with Guillain-Barre´ syndrome and other neurological complications suspected.
2014	The Cook Islands	932 suspected, 50 confirmed cases	
2014	New Caledonia	1400 confirmed cases (35 imported)	
2014	Easter Island	51 confirmed out of 89 suspected cases from Jan - May 2014	Infecting strain closely related to viral strain found in French Polynesia
2015	Latin America[a]	Estimated 1.5 million cases in Brazil.	Association with microcephaly and maculopathy suspected

[a] As of 10 February 2016. Includes Barbados, Bolivia, Colombia, Commonwealth of Puerto Rico, Costa Rica, Curacao, Dominican Republic, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Jamaica, Martinique, Mexico, Nicaragua, Panama, Paraguay, Saint Martin, Suriname, U.S. Virgin Islands, Venezuela.

Transmission Cycles, Vector and Reservoirs: In Africa and Asia, ZIKV is maintained in a sylvatic environment, in a zoonotic cycle between mosquitoes (*Aedes* spp. and other species) and non-human primates. ZIKV antibodies have been detected in large mammals and in rodents, but the role of these animals as virus reservoirs [34].

The first vector ZIKV isolate was obtained in 1948 from *A. Africanus* [17]. Since then, ZIKV has been isolated from several different mosquito species in nature: *A. africanus, A. furcifer, A. luteocephalus, A. vittatus, A. dalzieli, A. hirsutus, A. metalicus A. taylori, A. aegypti, A. unilineatus, Anopheles coustani, Culex perfuscus,* and *Mansonia uniformis* in Africa. *A. aegypti* was suspected to have an important role in the urban transmission (mosquito-human-mosquito) of ZIKV in Nigeria due to the high prevalence of ZIKV antibodies in the urban population of Nigeria [16, 17, 18]. In Asia, further evidence incriminated *A. aegypti* as the urban vector after ZIKV was identified in a mosquito pool collected in Malaysia [19]; furthermore, in Indonesia, the peak in human ZIKV infections coincided with a peak in the *A. aegypti* population [34]. The virus is transmitted from life-long infected female mosquitos to humans during a blood meal. Because some male mosquitos have been found to be positive for ZIKV, vertical transmission might also occur [35].

Despite the recent ZIKV-related human epidemics observed in the Yap Islands, French Polynesia and the Americas, little is known about the mosquito vectors implicated in these events and their competence in transmitting ZIKV to humans. During the Yap Island epidemic, *A. hensilli* was implicated as the potential vector because it was the predominant species identified in local water-holding containers, although ZIKV has never been isolated from this mosquito species or from any other less abundant mosquito pools [36]. Because *A. aegypti* and *A. Polynesiensis* are highly prevalent in French Polynesia, by association; the former species was incriminated as the urban ZIKV vector throughout the 2013 epidemics [37, 38]. Boorman *et al*., demonstrated that *A. aegypti* mosquitoes that were artificially fed ZIKV were able to transmit the virus to both mice and monkeys under laboratory Conditions [39].

Presently, South and Central American countries are experiencing an enormous ZIKV epidemic [40]. Brazil displays high infestation rates of both the widely distributed *A. aegypti* and *A. albopictus.* The former species is the principal vector for DENV [41], and the latter has been demonstrated to be competent to transmit CHIKV [42]; both of these viruses co-circulate simultaneously with ZIKV within Brazilian territory [40, 41, 43]. *A. aegypti* populations are susceptible to ZIKV infection *in vitro* [44], and their role as the ZIKV primary vector in nature is being investigated. It remains to be determined whether mosquito species other than *Aedes spp*., and with different ecological behaviors, could be involved in urban ZIKV transmission in Brazil.

Transmission: The transmission of ZIKV typically occurs through the bite of an infected female mosquito during its blood feeding. In addition to the arthropod vector bite, perinatal ZIKV transmission has been described, and viral RNA has been detected in breast milk in two cases [45]. Caution should also be taken regarding the risk of Contamination by blood transfusion for ZIKV and other arboviruses that co-circulate in the American continent, such as DENV and CHIKV [46].

ZIKV was isolated from the semen of a patient several weeks after the acute phase of the disease [47], and a case of sexual transmission has been reported [48]. Since The risk of sexual transmission of ZIKV exists; there is a recommendation that man who reside in or have travelled to an area of active ZIKV transmission might consider the sexual abstinence or condom use during sexual intercourse, especially if his partner is a pregnant woman [49]. ZIKV RNA and/or protein has also been detected in urine [50], saliva [51], amniotic fluid [52] and placental tissues [53], highlighting the possibility of other modes of transmission. More recently, infective viral particles have been detected in the saliva of two individuals who tested positive for ZIKV, opening the possibility of another mode of person-to-person transmission (Bonaldo *et al*., unpublished data).

Travel Health Advice on Zika Virus by Who:

National Authorities:

In the context of Zika virus, countries are advised that:

There should be no general restrictions on travel or trade with countries, areas and/or territories with Zika virus transmission.

Standard WHO recommendations regarding vector control at airports should be implemented in keeping with the IHR (2005). Countries should consider the disinsection of aircraft.

With regard to surveillance, health workers and the health sector should be on alert specifically for Zika virus disease in travellers returning from affected countries. It is important that travellers and health care practitioners are informed on a range of issues before, during and after travel to areas with Zika virus transmission. Health authorities should:

Provide up-to-date advice to travellers on how to reduce the risk of becoming infected, including preventing mosquito bites and practicing safer sex.

Advise travellers from areas with ongoing Zika virus transmission to practice safer sex and not to donate blood for at least 1 month after return, to reduce the potential risk of onwards transmission.

Advise pregnant women not to travel to areas with ongoing Zika virus transmission.

Advise pregnant women whose sexual partners live in or travel to areas with ongoing or recent Zika virus transmission to ensure safe sexual practices or abstain from sex for the duration of their pregnancy.

Alert health care practitioners to the possibility of Zika virus infection in symptomatic travellers with a recent history of travel to areas of known, ongoing Zika virus transmission and areas at risk of transmission.

Provide health care practitioners with clear guidance on how to refer travellers with suspected Zika virus infection to appropriate management and testing.

Health Care Practitioners:

Health care practitioners advising travellers should: Provide travellers to areas with ongoing Zika virus transmission with up-to-date advice on how to reduce the risk of becoming infected, including preventing mosquito bites and practicing safer sex.

- Advise travellers to practice safer sex and not to donate blood for at least 1 month after return, to reduce the potential risk of onwards transmission.
- Advise pregnant women not to travel to areas with ongoing Zika virus transmission.
- Advise pregnant women whose sexual partners live in or travel to areas with ongoing Zika virus transmission to ensure safer sexual practices or abstain from sex for the duration of their pregnancy.
- Health care practitioners treating patients who have returned from areas with ongoing Zika virus transmission should:
- Consider Zika virus infection in patients with acute fever, rash, arthralgia, or conjunctivitis, who have travelled to countries affected by Zika virus in the 2 weeks prior to onset of illness.
- If Zika virus is suspected, send appropriate samples for testing (together with a full travel and clinical history with relevant dates) as early as possible to the relevant reference laboratory.
- Report suspected cases of Zika virus disease to the relevant state or local health authorities.
- Be alert for any increase in neurological syndromes, autoimmune syndromes or congenital malformations in neonates born to parents with a history of travel to areas with Zika virus transmission.
- Assess and monitor pregnant women who have travelled to areas with Zika virus transmission.
- Evaluate fetuses and infants of women infected with Zika virus during pregnancy for possible neurological syndromes or congenital malformations.

Clinical Manifestations: Historically, ZKV presents as a mild or in apparent form of dengue-like disease with myalgia, arthralgia, fever, conjunctivitis, maculopapular rash, headache, and prostration. Given the overlapping clinical manifestations of Zika, chikunguniya, and dengue virus, differentiates between the aforementioned viruses.

While severe disease requiring hospitalization from ZKV is uncommon, data from the French Polynesia epidemic documented a concurrent epidemic of 73 cases of Guillain–Barré syndrome and other neurologic conditions, which may represent complications of ZKV [54]. The latest 20-fold increase in the Brazilian epidemic of microcephaly, from 2014 to 2015, has led public health officials to postulate that the cause may be ZKV infections in pregnant women. Reports of seeing calcifications in fetal brain and placenta have been documented using ultrasonography.

While no other virus of the Flaviviridae family is identified to have teratogenic effects, the microcephaly epidemic has yet to be linked to any other cause. Even with the lack of any definitive proof of a direct relationship, health officials recommend all expecting women take precautions in avoiding mosquito bites and even to delay pregnancy.

According to a preliminary analysis of research carried out by the Brazilian health ministry, the greatest risk of microcephaly and malformations appears to be associated with infection during the first trimester of pregnancy. Furthermore, these health authorities in conjunction with the Pan American Health Organization are conducting research to clarify the cause, risk factors, and consequences of microcephaly [54]. Other sporadic literature has reported patients with hypertensive iridocyclitis and macular degeneration attributed to ZKV, as well as, the virus being sexually transmitted, with the latest report coming from Dallas, Texas [55, 56, 57].

TABLE 3: CLINICAL MANIFESTATIONS OF CHIKUNGUNYA, ZIKA, AND DENGUE VIRUS

Symptoms	Chikungunya	Zika	Dengue
Headache	*	*	***
Arthralgia	***	*	*/-
Myalgia	**	*	***
Conjunctivitis	**	***	-
Fever	**	*	***
Maculopapular Rash	**	***	*
Dyscrasia	*/-	-	**
Thrombocytopenia	*/-	*/-	***
Shock Syndrome	*/-	-	***
Hepatomegaly	***	-	-
Edema of Extremities	-	**	-

*** High Intensity; ** Medium Intensity; * Low Intensity; (-) Absent

Pathogenesis: ZKV is a mosquito-borne flavivirus related to dengue virus, yellow fever virus, and West Nile virus. ZKV is a single-stranded positive RNA virus (10,794-nt genome), which is closely

related to the Spondweni virus and is transmitted by several *Aedes* mosquitoes, including *Aedes. africanus*, *Aedes. hensilli*, *Aedes. luteocephalus*, *Aedes. Aegypti etc.* ZKV was first recognized in rhesus monkeys in 1947 during the sylvatic yellow fever surveillance in Zika Forest of Uganda, and reported in humans in 1952 [58, 59]. Of the two known lineages of the ZKV (African and Asian), Phylogenetic studies indicate that the closest strain of ZKV to that which, emerged in Brazil, was isolated from samples taken in French Polynesia and spread among the Pacific Islands, and belongs to the Asian lineage [60].

The human epidermal keratinocytes, dermal fibroblasts, and immature dendritic cells are permissive to the most recent ZKV isolate, responsible for the French Polynesia epidemic [61]. The virus next moves to the lymph nodes where autophagosomes may form causing enhanced viral replication and viremia [61]. The notorious association of the virus and newborn microcephaly remains to be independently confirmed and verified.

ZKV has been reported in human blood as soon as the day of the illness, while the viral nucleic acid has been detected until 11 days post onset. Ether, potassium permanganate, and temperatures >140°F (>60°C) have reportedly eliminated ZKV, whereas, 10% ethanol has failed to neutralize the virus [62].

Diagnosis: ZIKV Diagnosis of ZIKV infection is complicated by the fact that it is asymptomatic in up to 80% of cases. Symptoms that do occur tend to be mild and non-specific, including headache, fever and rash [20, 8]. Similarity in symptoms to those of other flavivirus infections, such as DENV further complicates diagnosis. Dating of the onset of symptoms tends to be complicated by the fact that there is no abrupt clinical onset [47]. There is, as yet, no gold standard laboratory diagnostic method available. Diagnosis during the acute phase of the illness is by detection of viral RNA in serum by reverse transcription PCR (ZIKV RT-PCR) [63]. For example, during the outbreak in Yap Island, a real-time RT-PCR test targeting the viral envelope gene was used [21]**.** Another envelope targeting test using degenerate primers was designed based on samples from West Africa [64]. A more recently developed test, which has the potential to be converted to a real time platform, was designed to target the highly con-served NS5 gene [65].

The short viremic period of ZIKV limits the utility of molecular diagnostic techniques on serum samples to a window of approximately 3−5 days following the onset of infection. ZIKV can also be detected in saliva samples by ZIKV RT-PCR at a higher rate than for blood samples, but it does not extend the window of time during which the virus can be detected [47, 63]. Saliva samples provide an alternative or additional sample to blood, which could be particularly useful in circumstances in which blood sample collection is difficult, for example with infants and young children [47]. ZIKV can also be detected by RT-PCR on urine samples, which may allow an extension of the detection window.ZIKV appears to be detectable in urine for more than 10 days after the onset of disease [47, 63, 50]. ZIKV diagnosis can also be achieved by detection of ZIKV-specific IgM and/or IgG antibodies via ELISA or immunofluorescence, starting from day 5 or 6 after the onset of symptoms [63].

However, results need to be interpreted carefully due to cross-reactivity in patients with previous flaviviral infections; particularly DENV [21, 20, 63, 8]. Recently, the release of a commercial kit for serological detection of ZIKV by ELISA and indirect immunofluorescence is available by EUROIMMUN. This is in keeping with the global response strategy outlined by WHO, which prioritizes development of a reliable, affordable and rapid diagnostic test [66, 67].

Guidelines for Pregnant Women during the Zika Virus Outbreak: Zika virus is attracting worldwide attention and everyone fears its potential dramatic effects on the fetal brain. The US Centers for Disease Control and Prevention (CDC) have recently published interim guidelines on management of pregnant women exposed to Zika virus [64]. We do, however, have some comments on these recommendations.

The guideline proposes to offer amniocentesis, as early as 15 weeks gestation, to pregnant women with a history of recent travelling to or living in a country with ongoing Zika virus circulation and presenting positive or inconclusive Zika virus testing or ultrasound findings compatible with a

Zika virus infection. In endemic areas, Zika virus co-circulates with other flaviviruses and serological cross-reactions responsible for false positive IgM detections are frequent. Since confirmation neutralizing antibody testing is restricted to highly specialized laboratories, a high number of positive or inconclusive Zika virus IgM results are expected, leading to unnecessary amniocenteses and related risk of miscarriages [65]. The sensitivity of molecular detection of Zika virus in the amniotic fluid is not known. It is highly likely that, by analogy with cytomegalovirus or toxoplasmosis Infections, the virus is only shed in the amniotic fluid once the fetal kidneys produce sufficient urine (*i.e.*, after 18 - 21 weeks gestation) and once sufficient time has elapsed for the virus to breach the placental barrier (at the earliest 6 - 8 weeks after infection) [66, 67].

To prevent false-negative results and false reassurance of the parents, we would therefore suggest offering amniocentesis only in the presence of fetal signs or 6–8 weeks after suspected maternal exposure, and not earlier than 21 weeks gestation with further close ultrasound follow-up of microcephaly and brain lesions in fetuses developing in the presence of Zika virus in the amniotic fluid is not known.

In view of this uncertainty, it is highly questionable whether amniocentesis, which carries a 0·1–1% risk of miscarriage, [65] is at all useful in the asymptomatic fetus. A normal result might not bring reassurance, and the presence of Zika virus in the amniotic fluid might not necessarily be associated with fetal brain damage. Miscarriages related to amniocentesis and pregnancies termination of asymptomatic fetuses might be much greater than the number of truly affected children. If counseled appropriately, many couples might decline the procedure, or at least wait until 21 Weeks's gestation. Additionally, since asymptomatic blood donors can still be viraemic for Zika virus, [68] we also recommend transfusing pregnant women only with products tested negative for Zika virus when those are collected locally.

Clinical Presentation: Asymptomatic patients are frequent, reaching up to 80%, and they constitute a high-risk source of transmission [68]. The incubation period ranges from 3 to 12 days, followed by a mild "dengue-like" syndrome for a period of 2 to 7 days with a broad range of symptoms, including the presence of huge maculopapular rashes, a state of mild fever and headaches, arthralgia, retro-orbital pain, conjunctivitis and edema of the extremities [20, 69, 9]. The eruption of maculopapular rashes presented by more than 90% of patients remains the main clinical symptom that characterizes ZIKV infection [70].

While the majority of human cases were benign, during the French Polynesian epidemic several neurological complications were reported presenting Guillain-Barré Syndrome (GBS), an autoimmune disease, due to damage to the peripheral nervous system with a loss of the myelin insulation resulting in myalgia, facial palsy and muscle dysfunction. During the French Polynesian outbreak, a patient who presented with GBS was diagnosed with Zika fever. Following this first case, about 72 cases of GBS were reported with 40 patients being seropositive for the presence of the virus and link with ZIKV infection was put forward. The incidence resulted in an unexpected increase of GBS by 20 fold [71]. However, the direct relationship between the virus and GBS need to be confirmed because of co-circulation of DENV (serotype 1 and 3) and ZIKV during this outbreak. Recently, the peculiarity of the ZIKV outbreak in Brazil has shown for the first time a possible link between ZIKV infection in pregnancy and microcephaly of the fetus. Congenital microcephaly is 205 characterized by a fetal head circumference under the average for gestational age with the most common resulting disability being intellectual retardation and physical disability. The incidence of congenital microcephaly in Brazil has increased dramatically from approximately 150 cases per year between 2010 and 2015 to almost double that during the first 9 months of 2015.

Since then, cases have shot up to over 2000 in just a few months. Transplacental ability of ZIKV has been demonstrated by the presence of viral RNA in the amniotic fluid of pregnant women with fetal microcephaly [52]. In addition to microcephaly, the possible relation between ZIKV infection and hydrops fetalis and fetal demise has recently reported in the same region [72]. All these data suggest a possible materno-fetal transmission. Although maternal-fetal transmission has been

already described in DENV and WNV, no other flavivirus is known to have teratogenic effects. Nevertheless, the microcephaly epidemic in Brazil could also be linked to any other cause, such as other infectious or environmental agents. A recent study has revealed some ocular manifestations in three infants with microcephaly with one presenting with a macular neuroretinal atrophy [73].

However, further studies are needed to better define the outcomes of ZIKV infection during pregnancy. In this respect, although there is clear evidence of an increased number of cases of microcephaly in Brazil, it has been suggested that the number of suspected cases might be overestimated because of the diagnosis relying on low-specificity screening tests and the inclusion of mostly normal children with small heads [74] requiring a stricter application of standardized anthropometric techniques and confirmation of suspected cases by laboratory or radiological evidence. There are no specific treatments or vaccine available against ZIKV and the treatment remained only a symptomatic support. The main means to combat infection are based on vector control and bite prevention.

TABLE 4: BASIC INFORMATION ON ZIKA VIRUS

Symptoms
• Headache • Arthralgia • Myalgia • Conjunctivitis • Fever • Vomiting • Maculopapular Rash • Prostration • Edema of Extremities
Incubation Period
• 3-12 days
Treatment
• Conservative Management (bed rest, fluids, acetaminophen)
Prevention
• House screens • Air conditioning • Removal of debris • Repellents • Avoid mosquito bite during 1st week of illness to avoid human ⟹ mosquitos ⟹ human transmission

Guillain–Barré Syndrome (GBS) and Other Neurological Complications: Apart from the microcephaly cases, neurological complications have been reported as the most severe complications of the ZIKV infection. An increased incidence of GBS was noticed in countries experiencing recent outbreaks of Zika, such as French Polynesia, Brazil, Colombia, among others. In a case - control study recently published in, a strong association between Zika and GBS. In this series of 42 GBS patients diagnosed during the outbreak in French Polynesia, the large majority of patients had positive IgM or IgG antibodies (98 %), as well as neutralizing antibodies against Zika (100 %), compared to only 56 % in the control group (patients admitted to hospital with other syndromes). Additionally, symptomatic Zika was reported by 88 % of the GBS patients preceding the neurological symptoms. No other associated risk factor was observed. The clinical picture of the cases included a rapid progression of disease (1-15 days, with an average of 6 days from the beginning of symptoms to the nadir) and more frequently an electrophysiological pattern of acute motor axonal neuropathy (AMAN). The outcome was generally favorable, with only 38 % of patients admitted to the ICU, 22 % with progression to respiratory support, and no deaths. All patients were treated with immunoglobulin [75].

The GBS incidence in French Polynesia during the Zika outbreak was estimated to be 24/100,000 people infected, compared with 1-4/100,000 person-years globally. In the recent outbreaks in Polynesia and Brazil other neurological complications including encephalitis, myelitis, and optical neuritis have been observed [76].

Vaccine Development: In an important "Make in India" moment, scientists at a Hyderabad lab say they have developed the world's first vaccine against the Zika Virus. They say, in fact, that they have two.

The World Health Organisation has declared Zika and its suspected link to birth defects a global health emergency. More than 20 countries in Latin America have reported an outbreak and a rare case of the Zika virus being transmitted through sex has been reported in Texas, USA. As the world searches for a vaccine and other global companies take first steps on research, the Bharat Biotech International Limited in Hyderabad says it has patented the Zika vaccine.

"On Zika, we are probably the first vaccine company in the world to file a vaccine candidate patent about nine months ago," said Dr. Krishna Ella, Chairman and Managing Director, Bharat Biotech Ltd.

Effective vaccines exist for several viruses of the flaviviridae family, namely yellow fever vaccine, Japanese encephalitis vaccine, and tick-borne encephalitis vaccine since the 1930s, and dengue fever vaccine since the mid-2010s [77, 78, 79]. WHO experts have suggested that the priority should be to develop inactivated vaccines and other non-live vaccines, which are safe to use in pregnant women and those of childbearing age [80]. The NIH Vaccine Research Centre (U.S.) began work towards developing a vaccine for Zika per a January 2016 report [81].

Bharat Biotech International (India) reported in early February 2016, that it was working on vaccines for Zika [82] using two approaches: "recombinant", involving genetic engineering, and "inactivated", where the virus is incapable of reproducing itself but can still trigger an immune response with animal trials of the inactivated version to commence in late February [83]. As of March 2016, 18 companies and institutions internationally were developing vaccines against Zika, but none had yet reached clinical trials [80]. The first human trial for Zika vaccine, a synthetic DNA vaccine (GLS-5700) developed by Inovio Pharmaceuticals, is approved by FDA in June 2016. Interim results of the Phase 1 study is expected in later 2016 [84]. Nikos Vasilakis of the UTMB predicted that it may take two years to develop a vaccine, but ten to twelve years may be needed before an effective Zika vaccine is approved by regulators for public use [85].

A single dose of two distinct vaccine candidates (DNA and inactivated virus vaccine) protected mice against the Zika virus [86].

Treatment: No specific treatment is available for ZKV. Supportive care includes rest, antipyretics, analgesics, and watching for coagulopathy or multi-organ failure are important goals of care. Antihistamines may be considered for cutaneous symptoms. Intravenous fluids, oxygen (as needed), and monitoring vital sign are further measures of care. Given the similarities in the symptoms and geographic distribution, suspected cases of ZKV should be assessed and managed for possible dengue or chikungunya virus infection. Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin should be delayed until dengue can be ruled out to reduce the possibility of hemorrhagic complications.

Prevention and Control: Successful vaccine development has been achieved for other flavivirus such as yellow fever or Japanese encephalitis. It has taken over 20 years for developing a dengue vaccine candidate available for clinical use and only in the past years Phase III studies have been performed [87]. To date no vaccine against Zika fever is available and it is anticipated that it will take several years for reaching full production. However, ZIKV vaccine might benefit from other flavivirus vaccine candidates and clinical testing could begin earlier than it is usual in vaccine development [88]. Thus, management of the mosquito is the only current available method for controlling ZIKV epidemic.

Mosquito control has been previously successful, though the persistence of pockets of mosquitoes leads to rapid re-emergence of arboviral diseases. Mosquito control relies on the use of insecticides and the removal of larval breeding sites. Due to the current wide spread resistance to insecticide, including pyrethroids [89, 90] and the difficulties on eliminating breeding sites at a city-scale, the capacity for containing the disease is substantially limited.

New approaches targeting the vector have been developed and are currently under investigation. Release of genetically modified male mosquitoes that compete with wild type males to mate females resulting in transmission of lethal genes (RIDL strategy) has shown promising results, with off spring incapable to reach adult stage and reducing 80 - 95% of population in the field [90]. An alternative approach is the introduction of the endosymbiont bacteriumWolbachia into *A. aegipti*. Wolbachia infected mosquitoes have shown relative resistance to flavivirus infection such as dengue or yellow fever through inhibition of replication and without impact on the mosquito fitness [91]. Interestingly, infected mosquito's can

displace natural populations and could lead to a potential introduction of natural biological resistance to flavivirus infection.

Individual preventive measures include the use of DEET- and picaridin-based repellents and minimizing day biting of *Aedes* mosquitos.

CONCLUSION: The review showed that the Zika virus has a structure similar to other flaviviruses, including dengue and West Nile viruses, with a core of genetic material in the form of RNA, encased inside a fatty membrane. This sits within a 20-sided protein shell covered in carbohydrates, known as glycans. But these glycans and their surrounding amino acids differ between the flaviviruses - and Zika, the scientists discovered, is no exception. The structure of the virus provides a map that shows potential regions of the virus that could be targeted by a therapeutic treatment, used to create an effective vaccine or to improve our ability to diagnose and distinguish Zika infection from that of other related viruses.

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