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Review Article

Zika Virus Infection: No Longer a Public Health Emergency of International Concern, an Update and Future Trend

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Abstract: Zika virus (ZIKV), a flavivirus known since 1947 and spread by Aedes mosquitoes is an arbovirus responsible of ZIKV infections with normally mild clinical symptoms. It's only since its outbreak in Brazil from when it is considered as serious problem with public health emergency and international concern; thus it appears to be associated with congenital microcephaly accompanied by grave outcomes. Fortunately, at the end of 2016 the ZIKV epidemic starts to decline, resulting in the end of World Health Organization's zika virus consideration as a problem of public health emergency. Here, we reviewed the transmission, clinical essentials and prevention of ZIKV infection by highlighting the reason behind of zika decreasing, but also the future perspective regarding vaccine and therapy against this virus.
Keywords: zika virus, *aedes aegypti*, World Health Organization, microcephaly, prevention.

INTRODUCTION

Recently since 2015 there has been a prompt and a quick emergence of ZIKV in different part of the World especially in Americas. This outbreak has pushed the World Health Organization (WHO) to declare ZIKV epidemic as a public health crisis of the world at the beginning of February 2016 [1], highlighting that this epidemic is considered to be a major threat to the whole world. Their statement of intent included the lines: Appropriate research and development efforts should be intensified for ZIKV vaccines, therapeutics and diagnostic; and national authorities should ensure the rapid reporting and timely sharing information of public health importance relevant to this WHO statement. Since then, many researchers have been interested in this virus which was considered before as not dangerous. In fact, ZIKV is an arthropod-borne virus (arbovirus) of the family Flaviviridae and genus Flavivirus [2]. It is related to the dengue, yellow fever, Japanese encephalitis, and West Nile viruses. Flaviviridae are small enveloped viruses (diameter of between 40 and 50 nm) hosting a positive-sense single-stranded RNA genome surrounded by an electron-dense nucleocapsid [3]. The complete genome is 9500–12,500 nucleotides long. It encodes a large polyprotein precursor, which is co- and posttranslationally processed by viral and cellular proteases into three structural proteins, building the capsid, and seven non-structural proteins involved in virus replication [4]. Information regarding pathogenesis of ZIKV is scarce but mosquito-borne flaviviruses are thought to replicate initially in dendritic cells near the site of inoculation then spread to lymph nodes and the bloodstream [5]. Although flaviviral replication is thought to occur in cellular cytoplasm, one study suggested that ZIKV antigens could be found in infected cell nuclei [6]. To date, infectious ZIKV has been detected in human blood as early as the day of illness onset; viral nucleic acid has been detected as late as 11 days after onset, thus the incubation period is typically 3–12 days [7].

The first isolation of ZIKV was made in April 1947 from the serum of a pyrexial rhesus monkey caged in the canopy of Zika Forest in Uganda. The second isolation was made from a lot of *Aedes africanus* taken in January, 1948, in the same forest. The virus has been called Zika virus after the locality from where the isolations were made for the first time [8]. From 1951 through 1981, serologic evidence of human ZIKV infection was reported from other African countries such as Egypt, Central African Republic, Sierra Leone and Gabon; some parts of Asia including India, Malaysia, the Philippines, Thailand, Vietnam, and Indonesia [9]; and in several islands of the pacific region since 2007 (Micronesia, Cook Islands, French Polynesia, New Caledonia, Guam, Samoa, Vanuatu and Solomon Islands) [1]. From that year, ZIKV has been considered as emergent: few cases have been described or reported since then [10].

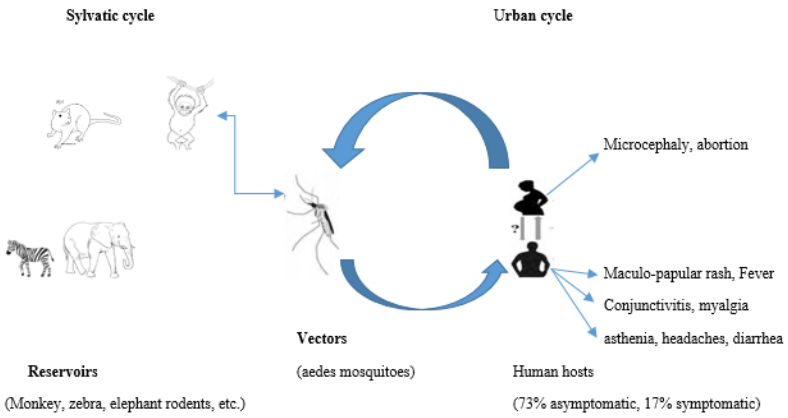
Since 2014, indigenous circulation of ZIKV has been detected in the Americas [11]. In Brazil, between January and July 2015, 121 cases of

neurological manifestations and Guillain-Barré syndrome have been notified in several north-eastern states with history of previous rash illness [12]. Investigations were launched and are on-going regarding possible association with ZIKV infection. In fact, even though there are no exact scientific proof regarding the association between ZIKV and microcephaly, different studies have been conducted to verify the potential association between them in Brazil ,Columbia and Slovenia [13]. A questioned surge in microcephaly prevalence occurred in 2015 (about 20 cases per 10,000 births), compared to that in previous years (about 1 case per 10,000 births); it reached its apogee in 2016, fortunately since the end of this year it starts to decline until now. This decreasing is linked to the preventive precautions focusing mainly on eradication of Aedes mosquitoes as there are neither vaccine nor curative treatment available for this virus [1].

In this review, we are going to highlight the reasons why ZIKV infection is no longer a public health threat, and discuss on how to repress another possible outbreak wherever it can appear.

Dynamics and mode of Transmission

In Africa, ZIKV has been isolated from *Aedes africanus* [8] and *Aedes luteocephalus* [14] , and in Malaysia from *Aedes aegypti* [15]. It has been isolated also from *Aedes apicoargenteus, Aedes vitattus* and *Aedes furcifer* mosquitoes; *Aedes hensilii* was the predominant mosquito species present on Yap during the ZIKV disease outbreak in 2007, but investigators were unable to detect ZIKV in any mosquitoes on the island during the outbreak [16]. The main vector associated with transmission of ZIKV especially in recent outbreak in Brazil is *Ae. aegypti* [17], which lives and breeds near people and their homes, laying their eggs in stagnant water which collects in puddles, buckets, flower pots, empty cans and other containers. They bite humans mainly during daytime, either outside or inside their houses. In addition, in 2014 *A. albopictus* was present in 59 % of municipalities [18] and spread to 24 out of 27 states [19]; it can live in both urban and sylvatic habitats, including bromeliads, perforated bamboo internodes, and tree holes [20, 21]. Comparatively to *A. aegypti* that usually feeds on humans, *A. albopictus* species feed on wide range of hosts as it is endophagic and exophagic [21]. However, apart from Aedes mosquitoes, some Anopheles, Culex, Eretmapodites and Mansonia species have also been suggested as vectors [22]. The incubation period is about 10 days [23]. Apart from humans and primates; elephants, rodents, zebras, and orangutans can be a reservoir of ZIKV [24] (Fig.1). In addition to vector-borne transmission, ZIKV could potentially be transmitted by blood transfusion like other flaviviruses, and several affected countries have developed strategies to try and screen blood donors [25]. It has been reported that the ZIKV sexual transmission is possible; During a Zika virus outbreak in French Polynesia, ZIKV was identified and isolated from the semen of a patient in Tahiti when he underwent treatment for hematospermia [26]; it can persist at least for 6 months in the semen of patient after acute infection [27].Thus during studies on mice, it has been shown that ZIKV infection can cause some damages; the chronic inflammation of the tests and epididymides was resulted from type I interferon receptor-deficient mice with ZIKV infection [28]; the virus persisted several weeks in the male reproductive tract after the initial infection and lead to a decrease of testes size; the mice became infertile due to a complete destruction in testes morphology and the loss of stem like cells [29]. In 2016, The United States reports a case of sexual transmission of Zika infection in Texas [30]; one patient developed symptoms of illness after returning from the Bolivarian Republic of Venezuela; the second patient had not recently travelled outside of the United States, but subsequently developed symptoms after sexual contact with the traveler. Back in 2008, clinical and serologic evidence indicate that two American scientists contracted Zika virus infections while working in Senegal in 2008. One of the scientists transmitted this arbovirus to his wife after his return at home [31]. Vertical, maternal fetal transmission or perinatal transmission of Zika virus has also been reported. The likely routes of transmission are breastfeeding, close contact between mother and newborn through saliva and other body fluids exchange, and transplacental during delivery [32]. Mucocutaneous contact to the virus in infected blood or via monkey bite, hemodialysis or transplantation, are other possibilities to get the ZIKV [1].



Fig−1. The transmission cycle, vectors and clinical manifestations of ZIKV.

The transmission cycle of ZIKV encompasses sylvatic cycle and urban cycle. In the sylvatic cycle, rhesus monkey is a corroborated ZIKV reservoir with the reality that a live ZIKV strain has been isolated from it. It is highly suspected that orangutan, zebra, elephant, and rodent are probable ZIKV reservoirs with regard to the detection of anti-ZIKV antibody in these animals. The transmission vectors of ZIKV are *Aedes* mosquitoes, especially *Aedes albopictus* and *Aedes aegypti*. Sexual transmission of ZIKV has been suggested, though currently, the cases are all involved in transmission from infected males to females. Most human infections (up to 73%) are asymptomatic, and in the apparently presented Zika cases, fever, maculopapule, arthralgia, nausea, diarrhea and even complications such as GBS and microcephaly are reported.

Zika virus disease

Zika virus infections has been long considered as asymptomatic as the majority (about 73% cases) doesn't show any clinical manifestation [16]. In case of symptomatic condition, symptoms appear after an incubation period of a few days after the bite of an infected mosquito and usually lasts 3 to 12 days, and are dengue-like syndrome and difficult to distinguish from dengue and chikungunya infections. Therefore, the main symptoms include: low-grade fever (<38.5°C), transient arthritis/arthralgia with possible joint swelling mainly in the smaller joints of the hands and feet, maculo-papular rash often spreading from the face to the body, conjunctival hyperemia or bilateral non-purulent conjunctivitis; general non-specific symptoms such as myalgia, asthenia, headaches and digestive disorder including nausea, vomiting, diarrhea, constipation, abdominal pain and ulcers [21]. Association with neurological complications such as Guillain-Barré syndrome and microcephaly has been suspected during the French Polynesia outbreak and very recently in Americas especially in Brazil and remains under investigation [13, 33]. Despite mild clinical symptoms, ZIKV infection during pregnancy appears to be associated with grave outcomes, including fetal death, placental insufficiency, fetal growth restriction, and Central Nervous System injury [34]. Microcephaly is the most common clinical presentation of congenital Zika syndrome, neonates and fetuses with suspected ZIKV infection are also found to have some other malformations including low birth weight, anasarca, unnecessary scalp skin, polyhydramnios and arthrogryposis. Neurological complications may also exist encompassing polymalformative syndromes, cerebral lesions, brainstem dysfunction and absence of swallowing. Ophthalmological deficiencies include cataract, intraocular calcifications, asymmetrical eye sizes, optic nerve hypoplasia, macular atrophy, iris coloboma and lens subluxation. However, further studies are needed to confirm with certainty the association of ZIKV and above congenital neurological symptoms as different etiologies with congenital anomalies outcomes exist and can misguide the diagnosis. As a matter of fact, there are numerous etiological agents related to microcephaly including genetic disorders, drug intoxication of the pregnant woman (i.e. use of alcohol, cocaine or antiepileptic drugs), maternal malnutrition and transplacental infections [1, 35, 36]. A study published on March 4, 2016 in the journal Stem Cell provided the first evidence of an existing biological connection between Zika and microcephaly [37]; it is reported that ZIKV infects human neural progenitor cells (hNPCs) derived from induced pluripotent stem cells. Infected hNPCs further release infectious ZIKV particles. Importantly, ZIKV infection increases cell death and dysregulates cell-cycle progression, resulting in attenuated hNPC growth. Global gene expression analysis of infected hNPCs reveals transcriptional dysregulation, notably of cell-cycle-related pathways. These results identify hNPCs as a direct ZIKV target. Furthermore, in collaboration with health officials in Brazil, the United States Centers for Disease Control and Prevention release laboratory findings (notified to WHO under IHR protocol) of four microcephaly cases in Brazil (two newborns who died in the first 24 hours of life and two miscarriages) which indicate the presence of Zika virus RNA by PCR and by immunohistochemistry of brain

tissue samples of the two newborns. In addition, placenta of the two fetuses miscarried during the first 12 weeks of pregnancy test positive by PCR. Clinical and epidemiological investigations in Brazil confirm that all four women presented fever and rash during their pregnancy [38]. Moreover, before the outbreak of 2015, there was no death associated to ZIKV, but in Brazil, three deaths have been observed, and one death of an adolescent with sickle cell anemia has been reported in Columbia [33, 35].

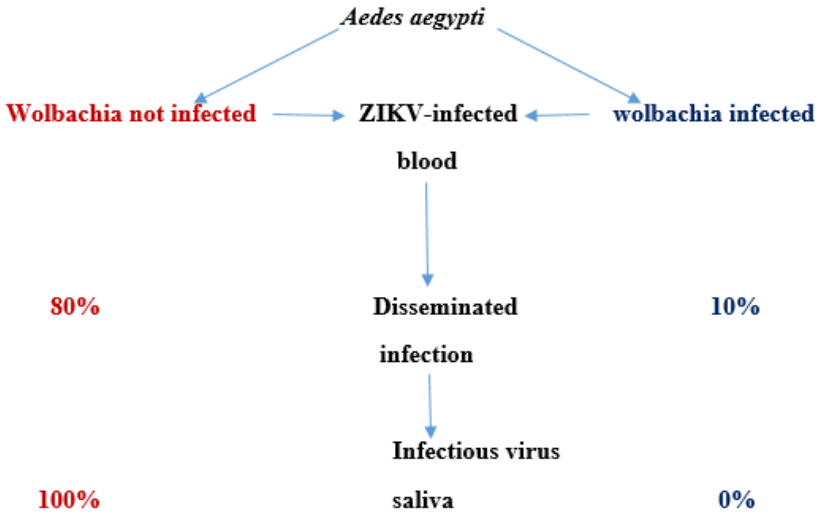
Prevention and treatment

There is no vaccine to prevent or specific medicine to treat Zika infections. Treatment is often not required for patients with asymptomatic or uncomplicated Zika fever [23, 33]; available therapeutic relies only on symptoms: getting plenty of rest, drinking fluids to prevent dehydration, taking medicine such as acetaminophen to relieve fever and pain; it is highly forbidden to take aspirin because of the risks of bleeding in those with thrombocytopenia [39]and increasing Reye's syndrome in children [33], all other non-steroidal anti-inflammatory drugs are prohibited because of the increased risk of hemorrhagic syndrome [22]. It has been reported that amodiaquine [1], an antimalarial drug that work via blockage of autophagy also inhibits Zika virus pathogenicity; in addition some of the drugs that target hepatitis C can have some special effects on ZIKV. A study has demonstrated that both amotosalen and ultraviolet A light combined lead to an inactivation of Zika virus in fresh-frozen plasma [40]. This inactivation process is of particular interest to prevent plasma transfusion-transmitted ZIKV infections in pandemic areas where several arboviruses are cocirculating.

Despite the huge interest in finding a therapeutic or preventive drug, there is no vaccine available for ZIKV. In 2016, it was reported that effective and safe Zika virus vaccine will probably be developed in next 3 to 10 years even with speedy research [21, 41]. In late 2015, the National Institutes of Health started an initiative for development of Zika virus, and Brazil has accelerated vaccine development. To date, the only way to treat ZIKAV is to prevent the risk of acquiring it. Center for disease control (US-CDC) in harmony with WHO have set different preventive measures; the first measure is to avoid mosquito bites by spraying insecticide in mosquito habitats, eliminating water reservoirs and containers because stagnant water acts as breeding site for Aedes mosquito, wearing long-sleeved shirts and long pants treated with permetthrin or another Environmental Protection Agency (EPA)-registered insecticide for extra protection , lodging in a room with air conditioning or screens on windows and doors, sleeping under a mosquito bed net,(Permethrin-treated bed nets provide more protection than untreated ones) [21, 41, 42].

People who wish to travel to ZIKV outbreak areas should also be educated on safe eating and drinking habits such as choosing bottled water over tap water, eating meat or seafood cooked fully, avoiding raw unpeeled fruits and vegetables, wearing appropriate footwear and avoiding skin contact with sand to prevent worm infections, such as cutaneous larva migrants. ZIKV is a blood borne disease and the infection control precautions include meticulous hand hygiene, standard and contact precautions (isolation, wearing gloves, water impermeable apron, protection of mucous membranes), safe disposal of sharps, blood and body fluids when patient are admitted to, or seen at healthcare facilities. It is particularly important that cleaning and sterilization of medical devices which are not disposable are carried out after each patient use [11]. Sexual partners who have traveled to stricken countries should use condoms and practice safe sex if their partner is pregnant. These measures should be maintained for the entire pregnancy as it is not clear when during gestation such infection can result in the significant brain injury. For those who are not pregnant, most can rest assured that they aren't likely to get symptomatic disease from Zika [39]. The above recommendations are highly advised to the pregnant women at any stage /semester.

Wolbachia pipientis, a bacterial endosymbiont of insect, has recently garnered attention as a mechanism for arbovirus control [43]. In fact, *Aedes aegypti*- harboring Wolbachia are highly resistant to infection with two currently circulating Zika virus isolates from the recent Brazilian epidemic (Fig.2); they don’t carry infectious viruses in saliva and therefore they can’t transmit them; this technique is being used in controlling zika extension in countries where ZIKV outbreaks have been reported, and has recently been recommended by the World Health Organization as a suitable tool to control ZIKV transmission (http://migre.me/tDWVe). On the other hand, the sterile insect technique (SIT) has been proposed to help in controlling the zika propagation. In fact, SIT has been used for over 50 years to suppress or eradicate a number of major insect pests. It uses ionizing radiation to sterilize male insects that have been mass-produced in special rearing facilities. The sterilized insects are then released over affected areas, where they mate with wild insects, producing no offspring [44]. As a result, the number of insects gradually decreases, leading to a reduction in the spread of the insect-borne diseases and damage.

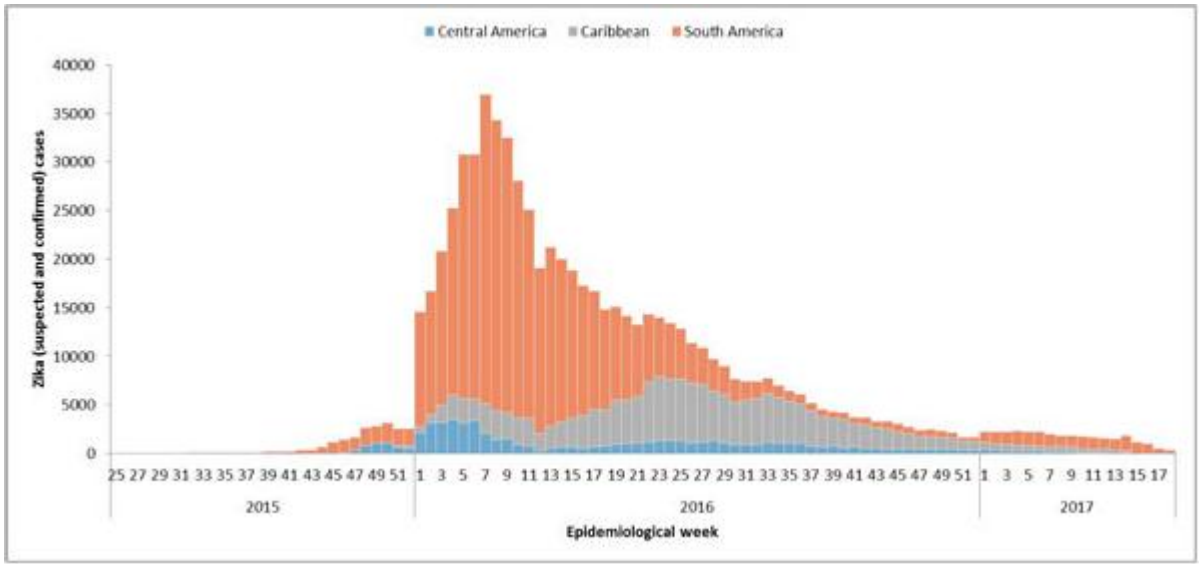


Fig−2. Blocking zika virus transmission with Wolbachia-harboring *Aedes aegypti*

While further research and field trials to study the effectiveness of the technique in the species of mosquitoes that spread the Zika are ongoing [45], the potential of introducing SIT as part of integrated mosquito control programs is being considered by several countries. Auto-dissemination strategy was also proposed recently to manage populations of *Aedes aegypti* and *Ae. Albopictus* [46, 47]. The method is based on coating wild females with Pyriproxyfen (PP), a juvenile hormone analog (JHA), using dissemination stations. When contaminated females lay eggs in larval sites, the insect growth regulator prevents adult metamorphosis of all larvae, including those originating from other non-contaminated females.

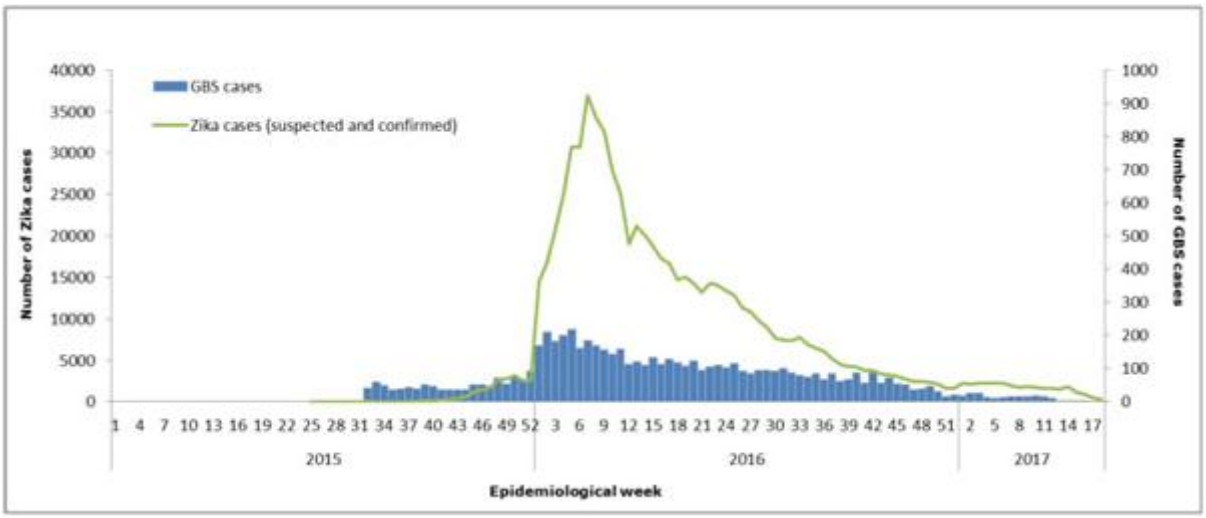
Basing on potential preventive highlighted above, we can now understand the reason behind of decreasing of new case of ZIKV infections and in congenital microcephaly observed in pandemic zones which were increasing incessantly by the beginning of onset to later 2016 (Fig. 3,4).

Brazil has used those techniques resulting in announcement of an end of its public health emergency over Zika in May 2017(https://www.theatlantic.com/news/archive/2017/05/brazil-ends-zika-emergency/526509/);before at the end of 2016 WHO had announced the same declaration; the health ministry said that from January to April 2017 there were 95 percent fewer cases recorded compared with that same period last year. But, while Brazil has declared an end to its emergency, the World Health Organization cautioned that Zika has not disappeared, and preventing another outbreak will require vigilance. Attention has to be continually made; vaccine and therapeutic research interests which were started since the outbreak in Americas need to go on. Various companies and academic organizations are using a variety of vaccine approaches, including inactivated virus, virus-like particles, nucleic-acid-based vaccines (DNA and RNA), live vectored vaccines, subunit vaccines, and live recombinant approaches [48]. The National Institutes of Health in United States announced in March 2017 that an experimental DNA vaccine is being tested in a clinical trial (49). This first phase will evaluate the vaccine's safety and ability to stimulate an immune response in a sample population of healthy men and non-pregnant women. It will also help to determine the optimal dose and injection sites for administration. Phase two aims to determine if the vaccine can effectively protect against Zika-related disease. At least 2,400 healthy men and nonpregnant women will receive either the investigational vaccine or a placebo and will be followed for nearly two years. Such ongoing and promising studies research either on vaccine or on relation between zika virus and congenital microcephaly [50] need more encouragement . ZIKV present high mutation rate, it varies between 12 and 25 bases a year, in a viral genome of 10 272 bases; this shows how much health practitioner and researcher in general have not to give up and continue to dig in purpose to block all doors from where this virus can remerge and cause more serious damages.



Fig−3. Distribution of suspected and confirmed Zika cases by Epidemiological Week (EW). Argentina, Brazil, Ecuador, and Peru, EW 25 of 2015 to EW 18 of 2017.

Statistics data from PAHO/WHO (http://www.paho.org/hq/index.php?option=com_content&id=11599&Itemid=41691 , accessed on 20th July 20, 2017)



Fig−4. Distribution of suspected and confirmed cases of Zika and GBS (Guillain-Barré syndrome) by Epidemiological Week (EW. Region of the Americas, 2015 – 2017 (as of EW 18)

Statistics data from PAHO/WHO (http://www.paho.org/hq/index.php?option=com_content&id=11599&Itemid=41691 , accessed on 20th July 20, 2017)

CONCLUSION

Preventive methods against ZIKV have proven their power by reducing the spread of this virus. This emerging flavivirus, was not deemed before to be a formidable threat to global public health due to the purportedly mild ailment it causes. However, with the recent spread of ZIKV infection throughout the world, the potential for this virus to induce a serious set of neural disorders has become evident and has pushed WHO to declare ZIKV infections as public health crisis of the world for almost a year. Even though ZIKV epidemic is no longer a Public Health Emergency of International Concern, it should be kept in mind that its future is unpredictable [51], the potential of emergence is very large and includes the entire tropical and subtropical world. However, the available prevention and control programmes has to be strengthened; ZIKV threats must be mitigated by priority actions such as improving integrated disease surveillance and response. Finally, improving the vaccine, therapy and diagnostic research on ZKIV have to be a must in order to understand the physiologic and molecular pathology of this virus, and enable the rapid development of a vaccine and antiviral treatments.

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