Chapter

Introductory Chapter: Zika 2015-2020 - Knowledge and Experience in the Americas

Carlos Andrés Rosero-Oviedo, D. Katterine Bonilla-Aldana, Jaime A. Cardona-Ospina, Wilmer E. Villamil-Gómez and Alfonso J. Rodriguez-Morales

1. Introduction

Zika virus is an arbovirus that was discovered many decades ago but remains fundamentally silent until a couple of decades ago. Nevertheless, only when arrived in the Americas, was able to cause significant epidemics and new clinical consequences, including microcephaly and the Guillain-Barré syndrome, among others. In this chapter, we introduce general concepts and our position regard the relevance of Zika and their knowledge and experience in the Americas over the last years, 2015–2020.

2. Fundamental aspects of Zika virus and Zika disease

The Zika virus (ZIKV) was first isolated in Uganda in 1947 and was confined for almost 60 years in Africa and Asia. Later, in 2007, the Yap outbreak allowed its spread to French Polynesia and other Pacific islands in 2013–2015, finally reaching the Americas in 2015 and being declared a Public Health Emergency of International Importance in 2016. Currently, no area is reporting Zika outbreaks; however, its circulation through sporadic cases remains a global threat. The discovery of ZIKV and many other arboviruses was the result of research conducted within the Rockefeller Foundation-sponsored yellow fever research programs [1]. The current East African Virus Research Institute (Entebbe, Uganda), was a focal point for research on pathogenic viruses. In April 1947, in an attempt to map the spread of yellow fever, the temperature of Rhesus monkeys, of the Asian species (*Macaca mulatta*), used in six sentinel platforms in the Zika forest in Entebbe, Uganda, was measured periodically [2]. On April 18, 1947, the temperature of one of these monkeys, Rhesus 766, was reported to be 39.7°C and the next day 40°C, so it was taken to the Entebbe laboratory where it was kept under observation for 30 days, with no evidence of other symptoms. On the third day of fever, a blood sample was taken that would subsequently allow the isolation of what was called ZIKV (strain 766). In the same report, the first isolation of ZIKV is described in 86 Aedes africanus mosquitoes trapped on a tree platform in the Zika forest in January 1948 [2]. Interestingly, although there was no evidence that ZIKV caused disease among Ugandan residents, the prevalence of antibodies to ZIKV was 9.5–20%, suggesting that the virus was already circulating in the human population (or was a consequence of cross-reactivity with other flaviviruses) [3]. A more detailed

description of the origins of ZIKV is presented elsewhere [4]. Although the initial isolation and characterisation of ZIKV in Uganda's Zika forest are unquestionable, there is some controversy as to which report described the first human ZIKV infection [5]. Several authors suggest that the first isolation in humans was in 1954, and it was a 10-year-old African girl with fever and headache associated with a malaria co-infection [6]. Cross-neutralisation tests with convalescent sera from monkeys infected with different viruses indicated that only ZIKV-infected serum neutralised the virus from the patient's serum, strongly suggesting ZIKV infection. However, a later published report indicated that the virus isolated in West Africa was more closely related to the Sponweni virus, and not to the Zika virus [7]. Ten years later, in 1964, a report is published of a worker at the East African Virus Research Institute in Entebbe who became infected with ZIKV while working on a series of new ZIKV strains, and his clinical presentation was characterised headache, diffuse pink maculopapular rash, myalgia, fever, and general malaise [8]. Interestingly, the author of the report is the same infected patient.

Outside of Africa, ZIKV was first isolated in 1969, in one of 58 groups of 1,277 *Aedes aegypti* mosquitoes collected from cities and towns on the Malay Peninsula (now Malaysia, Asia) [9]. Then, in 1977 in Indonesia (Asia), human infections of ZIKV infection were described, which were clinically characterised by high fever, malaise, stomach pain, dizziness and anorexia [10]. Notably, apart from direct evidence on ZIKV circulation from previously described human isolates and cases of infection, serological studies conducted in the 1950s suggest that ZIKV had a widespread distribution in both Africa (East, Central, West and South) as in several Asian countries [11]. However, the interpretation of serological results should be made with caution because the cross-reactions were not well characterised at that time [12]. From the first report of ZIKV infection in humans in 1954 (or 1964) through the early 2000s, only a few isolated cases of ZIKV infection disease have been documented. However, the outbreak in Yap State "initiates" the events that would make ZIKV a potential pandemic threat and are briefly described in **Figure 1**. Other publications describe these milestones in more detail [13–26].

The ZIKV is a member of the Flaviviridae family of viruses, which includes small viruses with a positive single-stranded RNA genome (9000–13000 bases) and which in turn is composed of 4 genera (Flavivirus, Hepacivirus [hepatitis C virus], Pegivirus and Pestivirus) [27]. Although transmission through mosquito bites is the

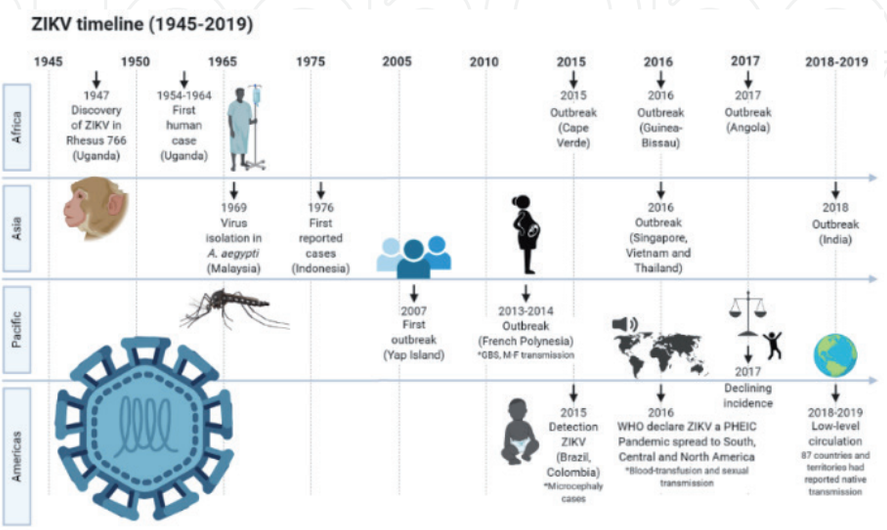


Figure 1.
*Chronology of ZIKV infection and reported cases. *ZIKV = Zika virus; GBS = Guillain-Barré syndrome; M-F = Maternal-fetal; PHEIC = Public Health Emergency of International Concern.*

primary mechanism for the spread of ZIKV, other routes of transmission have been proposed that contribute to the epidemic.

Vector transmission: Transmission through the bite of infected mosquitoes is the primary mechanism for the spread of ZIKV. The *Aedes aegypti* mosquito is the primary vector for urban transmission of ZIKV throughout the world. At the same time, other Aedes species can act as vectors for ZIKV in specific environments where its abundance is essential (e.g. *A. albopictus* that lives in temperate regions) [29]. Aedes mosquitoes can also transmit dengue and chikungunya viruses.

Non-vector transmission: Non-vector transmission events have been reported including maternal-fetal transmission, sexual transmission, transmission associated with transfusion of blood products or organ transplantation, and laboratory exposure [30, 31].

3. Clinical features

Possibly the first clinical description of a patient with ZIKV was reported in 1956 [32]. It was a 34-year-old European volunteer who was inoculated subcutaneously with a strain of ZIKV from Nigeria. After an incubation period of 82 hours, he developed a frontal headache associated with mild and short-term fever. On the afternoon of the fifth day, the headache, fever, and malaise increased in severity. It was accompanied by nausea and vertigo (which was attributed to a histamine reaction that responded to a small dose of aspirin). By the seventh day, the patient had fully recovered [32]. The percentage of asymptomatic ZIKV infections is estimated to be 50–80% [16, 33]. Data obtained from the Yap Island seroprevalence study showed that only 19% of those infected had symptoms attributable to ZIKV [34]. However, the retrospective seroprevalence study in French Polynesia showed that, among ZIKV seropositive patients, the percentage of symptomatic infections was 47% in adults [35]. That suggests that the virus strain could influence the proportion of symptomatic ZIKV infections.

For symptomatic infections, the incubation period varies from 3 to 14 days [36], and in most cases, the disease is self-limited [37]. It generally manifests as an itchy rash, mild fever, fatigue, myalgia/arthralgia, conjunctivitis, and headache, with an average duration of 1 week [37, 38]. The clinical characteristics appear to be similar in all age groups, regardless of sex and gestational status. Serious illness requiring hospitalisation is rare [9–48]. As observed, especially in some countries of Latin America, comorbidities would complicated cases [21–48].

The frequency of complications related to ZIKV infection appears to be low, but when they do occur, they are severe and can be fatal [39]. The most commonly reported complications to include complications associated with ZIKV infection during pregnancy such as congenital ZIKV syndrome (CZS), microcephaly, congenital malformations or abnormalities, brain abnormalities (e.g., delayed brain growth), eye disorders, pregnancy, fetal or perinatal death, hearing disorders, cardiovascular damage, neurological complications, intrauterine growth restriction, amniotic fluid abnormalities and epilepsy; neurological complications in adults, such as Guillain-Barré syndrome (https://www.who.int/csr/disease/zika/case-definition/en/); and finally death associated with ZIKV infection [40–49].

4. Diagnosis

Because the clinical manifestations of acute ZIKV infection are nonspecific, the definitive diagnosis is made by molecular and serological methods [43]. However, clinical and epidemiological criteria justify screening tests.

4.1 Clinical

For ZIKV disease, the clinical criteria for the definition of a suspected case according to the Centers for Disease Control and Prevention (CDC, 2016) corresponds to a person with one or more of the following (not explained by another aetiology) [15–44]:

Suspected case:

- Clinically compatible disease including acute onset of fever (measured or reported), maculopapular rash, arthralgia or conjunctivitis; or
- Guillain-Barré syndrome or other neurological manifestations; or
- Complications of pregnancy (e.g., loss of a fetus, fetus or newborn with congenital microcephaly, congenital intracranial calcifications, structural abnormalities of the brain or eyes, or structural abnormalities related to the central nervous system).

Epidemiological link criteria:

- Recent residence or travel to areas with known ZIKV transmission, sexual contact with a confirmed or probable case within the transmission risk window (2 weeks).
- Receipt of blood, blood products or organ or tissue transplantation within 30 days after the onset of symptoms.
- Association in time and place with a confirmed or probable case; and
- Probable vector exposure in an area with suitable ecological and seasonal conditions for possible local vector transmission.

*An online resource is available through the CDC website (https://wwwnc.cdc.gov/travel/page/zika-information) to recognise areas with reported cases of ZIKV infection.

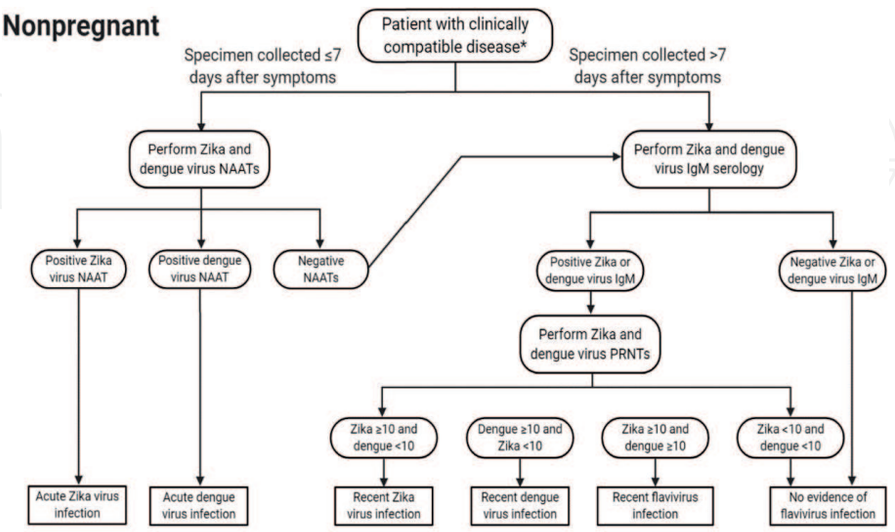
4.2 Laboratory

The diagnostic approach to ZIKV infection may vary depending on the resources available. For patients with suspected ZIKV disease, molecular detection of ZIKV RNA (e.g. nucleic acid amplification tests or NAAT [by RT-PCR]) is the preferred diagnostic method because they can provide confirmed evidence of infection and distinguish the specific virus [45, 46]. However, nucleic acid tests only show the presence of ZIKV RNA but do not necessarily indicate the presence of infectious viruses. On the other hand, serological tests (e.g. IgM antibodies [employing an immunosorbent assay linked to IgM antibody capture enzymes or MAC-ELISA]) or IgG [by plaque reduction neutralisation test or PRNT] against ZIKV are They are used mainly in patients who present after the viral nucleic acid is no longer detectable [20–48], despite the number of false-positive results due to cross-reactivity with other flaviviruses.

The algorithm for recommendations and the interpretation of the results of the dengue virus and ZIKV diagnostic tests are described in **Figure 2**.

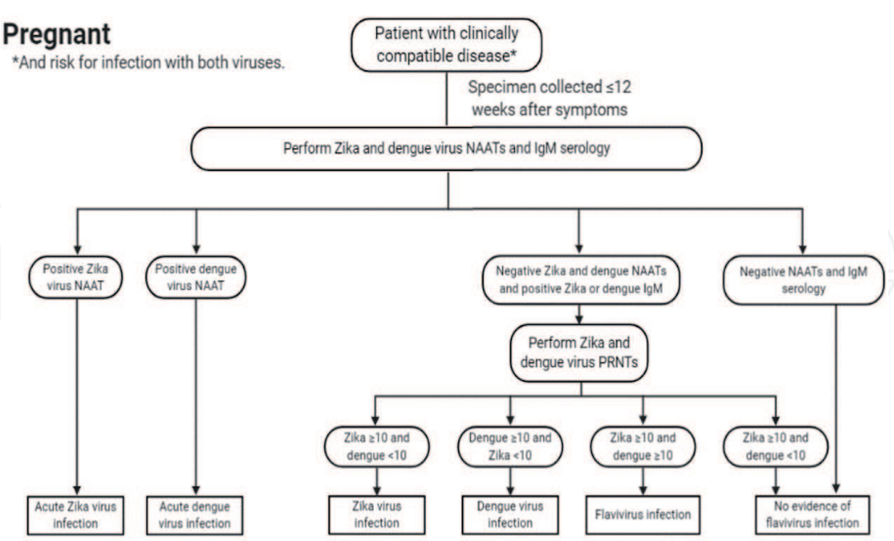
4.2.1 Pregnant women

Pregnant women with a clinically compatible disease and possible exposure to ZIKV or dengue virus should be evaluated as soon as possible (**Figure 3**). Evaluation for ZIKV and dengue infection is performed by performing NAAT and IgM antibody testing on serum sample and NAAT on a urine sample. NAATs can be performed on



NAAT = nucleic acid amplification test; PRNT = plaque reduction neutralization test. Selection of samples and tests: Dengue virus and ZIKV NAATs, IgM antibody tests and PRNTs must be performed on serum. Some NAATs can also be performed on plasma, whole blood, cerebrospinal fluid, or urine, and some antibody tests can be performed on plasma, whole blood, or cerebrospinal fluid. Laboratories may choose to test for Dengue virus and ZIKV IgM and NAAT antibodies simultaneously rather than sequentially, or to test Dengue virus nonstructural protein one rather than Dengue virus NAAT. Indications for repeat testing: If the patient's disease is of epidemiological or clinical significance (e.g., the first case of local transmission in the area, a new mode of transmission, or unusual clinical syndrome), repeat a positive NAAT on fresh RNA extracted from the same sample. For indeterminate results of the IgM antibody test, repeat the IgM antibody test or perform a PRNT on the same sample. In areas where PRNT is not performed, report indeterminate results and request a second serum sample for IgM antibody testing. Interpretation of results: Dengue virus and ZIKV IgM antibodies can be detected in serum during the months after infection. The specific time of infection cannot be determined. Data on the epidemiology of viruses known to circulate at the site of exposure and clinical findings should be taken into account when interpreting the results of serological diagnostic tests.

Figure 2.
*Algorithm of recommendations for testing ZIKV and dengue virus for people with the clinically compatible disease and risk for infection with both viruses. *And risk for infection with both viruses. Adapted and modified from CDC.*



NAAT = nucleic acid amplification test; PRNT = plaque reduction neutralization test. * Selection of samples and tests: Dengue virus and ZIKV NAATs, IgM antibody tests and PRNTs must be performed on serum. Some NAATs can also be performed on plasma, whole blood, cerebrospinal fluid, or urine, and some antibody tests can be performed on plasma, whole blood, or cerebrospinal fluid. Dengue virus NAAT does not need to be performed on samples collected> 7 days after disease onset. Some laboratories may choose to test dengue virus nonstructural protein one instead of dengue virus NAAT. Indications for repeat testing: If the ZIKV NAAT is positive in a single sample, but the IgM antibody tests are negative, repeat the NAAT on freshly extracted RNA from the same sample. For indeterminate results of the IgM antibody test, repeat the IgM antibody test or perform a PRNT on the same sample. In areas where PRNT is not performed, report indeterminate results and request a second serum sample for IgM antibody testing. Interpretation of results: Dengue virus and ZIKV IgM antibodies can be detected in serum during the months after infection. The specific time of infection cannot be determined. Data on the epidemiology of viruses known to circulate at the site of exposure and clinical findings should be taken into account when interpreting the results of serological diagnostic tests.

Figure 3.
*Algorithm of recommendations for testing ZIKV and dengue virus for pregnant women with the clinically compatible disease and risk for infection with both viruses. *And risk for infection with both viruses. Adapted and modified from CDC.*

plasma, cerebrospinal fluid whole blood, or amniotic fluid; likewise, IgM antibody tests can be performed on plasma, whole blood, or cerebrospinal fluid. Specimens should be collected as soon as possible and within 12 weeks of the onset of symptoms. A positive NAAT result in any sample provides sufficient evidence of a recent infection. However, suppose the NAAT is only positive for ZIKV in a single sample, and the IgM antibody test is negative. In that case, the NAAT should be repeated with fresh RNA from the same sample to rule out false-positive results. If the NAAT is negative, but the IgM antibody test is positive, confirmatory PRNTs should be performed for dengue, ZIKV, and other flaviviruses endemic to the region (**Figure 3**).

For asymptomatic pregnant women without continued risk of possible Zika virus infection, routine screening for ZIKV infection is not recommended. However, the assessment must be considered in terms of risk and through a shared decision-making model. A more detailed review is described elsewhere [15–39].

The algorithm of recommendations and the interpretation of the results of the dengue virus and ZIKV diagnostic tests in pregnant women are described in **Figure 2**.

5. Classification of cases

The definition of suspected cases was previously described. According to the CDC [44], suspected cases should be classified into:

Probable case	Confirmed case
• Clinical criteria for ZIKV disease; and • Epidemiological link; and • Laboratory evidence of recent ZIKV or flavivirus infection by: ○ Positive test of IgM antibodies against ZIKV in serum or CSF; and ○ Positive neutralising antibody titers (e.g. PRNT) against ZIKV, dengue or other flaviviruses endemic to the region where the exposure occurred; or ○ Negative test for IgM antibodies against dengue virus, and no neutralising antibody tests were performed.	• Clinical criteria for ZIKV disease; and • Laboratory evidence of recent ZIKV infection by: ○ Detection of ZIKV by culture, viral antigen or viral RNA in serum, CSF, tissue or another sample (e.g. amniotic fluid, urine, semen, saliva); or ○ Positive serum or CSF IgM antibody test against ZIKV with positive ZIKV neutralising antibody titers (≥10) and negative neutralising antibody titers against dengue or other endemic flaviviruses in the region of exposure.

[*] *The criteria for WHO/PAHO are similar (www.paho.org).*

6. Differential diagnostics

Differential diagnosis includes Dengue fever, Chikungunya virus, West Nile virus, Yellow fever, Malaria infection, Leptospirosis, Rubella, infectious Erythema (parvovirus B19 infection), Rocky Mountain spotted fever, Group A streptococcal infection, alphavirus infections, and coronavirus disease 2019 (COVID-19) [15–41]. Also, Mayaro, and the proposed ChikDenMaZika syndrome should be considered in the differential diagnostics [15–41].

7. Treatment of ZIKV disease

There is no specific treatment for ZIKV infection [15–43], and current treatment recommendations are based on limited evidence [15–44]. Thus, as with other

mosquito-borne flaviviruses, treatment for ZIKV infection is symptomatic and supportive and includes [15–45]:

7.1 Symptomatic and supportive treatment

- Rest and adequate hydration.
- Use of analgesics or antipyretics: Acetaminophen 325–1000 mg orally every 4 to 6 hours when necessary (maximum 4000 mg/day). Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided until dengue virus infection has been ruled out, to reduce the risk of bleeding.
- Calamine lotion can be used for the maculopapular rash.

* The management of pregnant women, congenital Zika syndrome, and Guillain-Barré syndrome is described in detail elsewhere [15–41].

Although a large number of existing drugs and novel chemical compounds have been postulated as possible interventions against ZIKV [15–46] and some have shown activity against ZIKV in animal and experimental models [15–48], none have yet demonstrated safety and efficacy in clinical trials [15-49]. A safety and tolerability trial for the monoclonal antibody against ZIKV called Tyzivumab (NCT03443830), and another for a polyclonal antibody against ZIKV (NCT03624946) have completed their recruitment phase and are currently in progress. At the moment, there are no treatments approved by government agencies for ZIKV, and there is no information to suggest that there are treatments in advanced stages of development [20–40].

8. Advances in vaccination

Significant efforts have been made to develop safe and effective vaccines against ZIKV. International scientific cooperation has resulted in multiple candidate vaccines that are now in various stages of clinical and preclinical development [22–42]. Several vaccines are being developed, including purified inactivated viral particles (PIV), purified virus-like particles (VLPs) and viral subunit proteins, live attenuated vaccines, chimeric vaccines, and viral and non-viral vectors that encode ZIKV structural proteins [20–43]. The most advanced candidate corresponds to a DNA vaccine (VRC5283) developed by the National Institute of Allergy and Infectious Diseases (NIAID) that is being evaluated in phase 2 clinical study (NCT03110770) that seeks to evaluate the safety and tolerability of the vaccine. (Phase A) and the safety and efficacy compared to placebo (Phase B); that is, the safety, immunogenicity, optimal dose of administration are evaluated, and an attempt will be made to determine the ability of the vaccine to prevent the disease caused by ZIKV infection effectively. At the time of this writing, the results published on www.clinical.trials.gov had not completed the quality control review process. However, its results have been promising [20–44]. However, significant challenges remain in the development of vaccines for ZIKV. Difficulties include the heterogeneity of the incidence of ZIKV infection, difficulties in financing, regulation and authorisation of vaccines, which in turn has limited the conduct of phase 2 and 3 clinical trials and prompted international organisations to consider approaches alternative, as models of infection by controlled human exposure [25–46]. Vaccine development for ZIKV is underway.

9. Conclusions

The impact and burden of Zika in the Americas region have multiple implications. Clinical and epidemiological research has been vital in the understanding and developing of knowledge for the management and prevention of this emerging arboviral disease [30–48]. Still, many challenges exist, including the developing of an effective vaccine, still under developing.

Author details

Carlos Andrés Rosero-Oviedo[1], D. Katterine Bonilla-Aldana[2,3], Jaime A. Cardona-Ospina[1,2,4], Wilmer E. Villamil-Gómez[5,6] and Alfonso J. Rodriguez-Morales[1,2,3,4,5*]

1 Grupo de Investigación Biomedicina, Faculty of Medicine, Fundación Universitaria Autónoma de las Américas, Pereira, Risaralda, Colombia

2 Public Health and Infection Research Group, Faculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Colombia

3 Semillero de Investigación en Zoonosis, Grupo BIOECOS, Fundación Universitaria Autónoma de las Américas, Pereira, Colombia

4 Emerging Infectious Diseases and Tropical Medicine Research Group, Instituto para la Investigación en Ciencias Biomédicas-Sci-Help, Pereira, Colombia

5 Infectious Diseases and Infection Control Research Group, Hospital Universitario de Sincelejo, Sincelejo, Sucre, Colombia

6 Programa del Doctorado de Medicina Tropical, SUE Caribe, Universidad del Atlántico, Barranquilla, Colombia

*Address all correspondence to: ajrodriguezmmd@gmail.com

References

[1] DICK, G. W. (1953). Epidemiological notes on some viruses isolated in Uganda; Yellow fever, Rift Valley fever, Bwamba fever, West Nile, Mengo, Semliki forest, Bunyamwera, Ntaya, Uganda S and Zika viruses. Transactions of the Royal Society of Tropical Medicine and Hygiene, Jan;47(1), 13-48. https://doi.org/10.1016/0035-9203(53)90021-2

[2] DICK, G. W., KITCHEN, S. F., & HADDOW, A. J. (1952). Zika virus. I. Isolations and serological specificity. Transactions of the Royal Society of Tropical Medicine and Hygiene, Sep;46(5), 509-20. https://doi.org/10.1016/0035-9203(52)90042-4

[3] DICK, G. W. (1952). Zika virus. II. Pathogenicity and physical properties. Transactions of the Royal Society of Tropical Medicine and Hygiene, Sep;46(5), 521-34. https://doi.org/10.1016/0035-9203(52)90043-6

[4] Campos, G. S., Bandeira, A. C., & Sardi, S. I. (2015). Zika Virus Outbreak, Bahia, Brazil. Emerging Infectious Diseases, Oct;21(10), 1885-1886. https://doi.org/10.3201/eid2110.150847

[5] Schuler-Faccini, L., Ribeiro, E. M., Feitosa, I. M., Horovitz, D. D., Cavalcanti, D. P., Pessoa, A., Doriqui, M. J., Neri, J. I., Neto, J. M., Wanderley, H. Y., Cernach, M., El-Husny, A. S., Pone, M. V., Serao, C. L., Sanseverino, M. T., & Brazilian Medical Genetics Society–Zika Embryopathy Task Force (2016). Possible Association Between Zika Virus Infection and Microcephaly - Brazil, 2015. MMWR. Morbidity and mortality weekly report, 65(3), 59-62. https://doi.org/10.15585/mmwr.mm6503e2

[6] Camacho, E., Paternina-Gomez, M., Blanco, P. J., Osorio, J. E., & Aliota, M. T. (2016). Detection of Autochthonous Zika Virus Transmission in Sincelejo, Colombia. Emerging infectious diseases, 22(5), 927-929. https://doi.org/10.3201/eid2205.160023

[7] Sarmiento-Ospina, A., Vásquez-Serna, H., Jimenez-Canizales, C. E., Villamil-Gómez, W. E., & Rodriguez-Morales, A. J. (2016). Zika virus associated deaths in Colombia. The Lancet. Infectious diseases, 16(5), 523-524. https://doi.org/10.1016/S1473-3099(16)30006-8

[8] WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. (2016). Retrieved November 23, 2020, from World Health Organization (WHO) website: https://www.who.int/news/item/01-02-2016-who-statement-on-the-first-meeting-of-the-international-health-regulations-(2005)-(ihr-2005)-emergency-committee-on-zika-virus-and-observed-increase-in-neurological-disorders-and-neonatal-malformations

[9] Zika situation report. (2016). Retrieveded November 23, 2020, from World Health Organization (WHO) website: https://www.who.int/emergencies/zika-virus/situation-report/31-march-2016/en/

[10] Zika epidemiology update. (2019). Retrieveded November 23, 2020, from World Health Organization (WHO) website: https://www.who.int/emergencies/diseases/zika/epidemiology-update/en/

[11] Simmonds, P., Becher, P., Bukh, J., Gould, E. A., Meyers, G., Monath, T., Muerhoff, S., Pletnev, A., Rico-Hesse, R., Smith, D. B., Stapleton, J. T., & Ictv Report Consortium (2017). ICTV Virus Taxonomy Profile: Flaviviridae. The Journal of general virology, 98(1), 2-3. https://doi.org/10.1099/jgv.0.000672

[12] Kuno, G., Chang, G. J., Tsuchiya, K. R., Karabatsos, N., & Cropp, C. B. (1998). Phylogeny of the genus Flavivirus. Journal of virology, 72(1), 73-83. https://doi.org/10.1128/JVI.72.1.73-83.1998

[13] Gutiérrez-Bugallo, G., Piedra, L. A., Rodriguez, M., Bisset, J. A., Lourenço-de-Oliveira, R., Weaver, S. C., Vasilakis, N., & Vega-Rúa, A. (2019). Vector-borne transmission and evolution of Zika virus. Nature ecology & evolution, 3(4), 561-569. https://doi.org/10.1038/s41559-019-0836-z

[14] Gregory, C. J., Oduyebo, T., Brault, A. C., Brooks, J. T., Chung, K. W., Hills, S., Kuehnert, M. J., Mead, P., Meaney-Delman, D., Rabe, I., Staples, E., & Petersen, L. R. (2017). Modes of Transmission of Zika Virus. The Journal of infectious diseases, 216(suppl_10), S875–S883. https://doi.org/10.1093/infdis/jix396

[15] Grischott, F., Puhan, M., Hatz, C., & Schlagenhauf, P. (2016). Non-vector-borne transmission of Zika virus: A systematic review. Travel medicine and infectious disease, 14(4), 313-330.

[16] BEARCROFT W. G. (1956). Zika virus infection experimentally induced in a human volunteer. Transactions of the Royal Society of Tropical Medicine and Hygiene, 50(5), 442-448.

[17] Baud, D., Gubler, D. J., Schaub, B., Lanteri, M. C., & Musso, D. (2017). An update on Zika virus infection. Lancet (London, England), 390(10107), 2099-2109. https://doi.org/10.1016/S0140-6736(17)31450-2

[18] Duffy, M. R., Chen, T. H., Hancock, W. T., Powers, A. M., Kool, J. L., Lanciotti, R. S., Pretrick, M., Marfel, M., Holzbauer, S., Dubray, C., Guillaumot, L., Griggs, A., Bel, M., Lambert, A. J., Laven, J., Kosoy, O., Panella, A., Biggerstaff, B. J., Fischer, M., & Hayes, E. B. (2009). Zika virus outbreak on Yap Island, Federated States of Micronesia. The New England journal of medicine, 360(24), 2536-2543. https://doi.org/10.1056/NEJMoa0805715

[19] Aubry, M., Teissier, A., Huart, M., Merceron, S., Vanhomwegen, J., Roche, C., Vial, A. L., Teururai, S., Sicard, S., Paulous, S., Desprès, P., Manuguerra, J. C., Mallet, H. P., Musso, D., Deparis, X., & Cao-Lormeau, V. M. (2017). Zika Virus Seroprevalence, French Polynesia, 2014-2015. Emerging infectious diseases, 23(4), 669-672. https://doi.org/10.3201/eid2304.161549

[20] Krow-Lucal, E. R., Biggerstaff, B. J., & Staples, J. E. (2017). Estimated Incubation Period for Zika Virus Disease. Emerging infectious diseases, 23(5), 841-845. https://doi.org/10.3201/eid2305.161715

[21] Musso, D., & Gubler, D. J. (2016). Zika Virus. Clinical microbiology reviews, 29(3), 487-524.

[22] Plourde, A. R., & Bloch, E. M. (2016). A Literature Review of Zika Virus. Emerging infectious diseases, 22(7), 1185-1192. https://doi.org/10.3201/eid2207.151990

[23] Cardona-Ospina, J. A., Henao-SanMartin, V., Acevedo-Mendoza, W. F., Nasner-Posso, K. M., Martínez-Pulgarín, D. F., Restrepo-López, A., Valencia-Gallego, V., Collins, M. H., & Rodriguez-Morales, A. J. (2019). Fatal Zika virus infection in the Americas: A systematic review. International journal of infectious diseases, 88, 49-59. https://doi.org/10.1016/j.ijid.2019.08.033

[24] Ximenes, R., Ramsay, L. C., Miranda, R. N., Morris, S. K., Murphy, K., Sander, B., & RADAM-LAC Research Team (2019). Health outcomes associated with Zika virus infection in humans: a systematic review of systematic reviews. BMJ open, 9(11), e032275. https://doi.org/10.1136/bmjopen-2019-032275

[25] Identification and management of Guillain-Barré syndrome in the context of Zika virus Interim guidance. (2016). Retrieved November 23, 2020, from World Health Organization (WHO) website: https://www.who.int/csr/resources/publications/zika/guillain-barre-syndrome/en/

[26] Lanciotti, R. S., Kosoy, O. L., Laven, J. J., Velez, J. O., Lambert, A. J., Johnson, A. J., Stanfield, S. M., & Duffy, M. R. (2008). Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. Emerging infectious diseases, 14(8), 1232-1239.

[27] Zika virus disease Interim case definition. (2016). Retrieved November 23, 2020, from World Health Organization (WHO) website: https://www.who.int/csr/disease/zika/case-definition/en/

[28] Furtado, G., & Scavuzzi, A. (2020). Zika virus infection. Retrieved November 23, 2020, from BMJ Best Practice website: https://bestpractice.bmj.com/topics/en-us/1302

[29] Clinical Evaluation & Disease. (2019). Retrieved November 23, 2020, from Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/zika/hc-providers/preparing-for-zika/clinicalevaluationdisease.html

[30] Zika virus. (2018). Retrieved November 23, 2020, from World Health Organization (WHO) website: https://www.who.int/news-room/fact-sheets/detail/zika-virus

[31] Epidemiological Update, Zika virus infection. (2015). Recuperado 23 de noviembre de 2020, de Pan American Health Organization (PAHO) website: https://iris.paho.org/handle/10665.2/50667

[32] LaBeaud, A. D. (2020). Zika virus infection: An overview. Retrieved November 23, 2020, from UpToDate website: https://www.uptodate.com/contents/zika-virus-infection-an-overview

[33] Barrows, N. J., Campos, R. K., Powell, S. T., Prasanth, K. R., Schott-Lerner, G., Soto-Acosta, R., Galarza-Muñoz, G., McGrath, E. L., Urrabaz-Garza, R., Gao, J., Wu, P., Menon, R., Saade, G., Fernandez-Salas, I., Rossi, S. L., Vasilakis, N., Routh, A., Bradrick, S. S., & Garcia-Blanco, M. A. (2016). A Screen of FDA-Approved Drugs for Inhibitors of Zika Virus Infection. Cell host & microbe, 20(2), 259-270.

[34] Bernatchez, J. A., Tran, L. T., Li, J., Luan, Y., Siqueira-Neto, J. L., & Li, R. (2020). Drugs for the Treatment of Zika Virus Infection. Journal of medicinal chemistry, 63(2), 470-489.

[35] Gorshkov, K., Shiryaev, S. A., Fertel, S., Lin, Y. W., Huang, C. T., Pinto, A., Farhy, C., Strongin, A. Y., Zheng, W., & Terskikh, A. V. (2019). Zika Virus: Origins, Pathological Action, and Treatment Strategies. Frontiers in microbiology, 9, 3252.

[36] G Viveiros Rosa, S., Fierro, I. M., & C Santos, W. (2020). Repositioning and investigational drugs for Zika virus infection treatment: a patent review. Expert opinion on therapeutic patents, 30(11), 847-862. https://doi.org/10.1080/13543776.2020.1811854

[37] Zika Virus Response Updates from FDA. (2020). Retrieved November 23, 2020, from United States Food and Drug Administration (FDA) website: https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/zika-virus-response-updates-fda

[38] Abbink, P., Stephenson, K. E., & Barouch, D. H. (2018). Zika virus vaccines. Nature reviews. Microbiology, 16(10), 594-600.

[39] Pattnaik, A., Sahoo, B. R., & Pattnaik, A. K. (2020). Current Status of Zika Virus Vaccines: Successes and Challenges. Vaccines, 8(2), 266.

[40] Poland, G. A., Kennedy, R. B., Ovsyannikova, I. G., Palacios, R., Ho, P. L., & Kalil, J. (2018). Development of vaccines against Zika virus. The Lancet. Infectious diseases, 18(7), e211–e219.

[41] Gaudinski, M. R., Houser, K. V., Morabito, K. M., Hu, Z., Yamshchikov, G., Rothwell, R. S., Berkowitz, N., Mendoza, F., Saunders, J. G., Novik, L., Hendel, C. S., Holman, L. A., Gordon, I. J., Cox, J. H., Edupuganti, S., McArthur, M. A., Rouphael, N. G., Lyke, K. E., Cummings, G. E., Sitar, S., ... VRC 320 study teams (2018). Safety, tolerability, and immunogenicity of two Zika virus DNA vaccine candidates in healthy adults: randomised, open-label, phase 1 clinical trials. Lancet (London, England), 391(10120), 552-562.

[42] Wilder-Smith, A., Vannice, K., Durbin, A., Hombach, J., Thomas, S. J., Thevarjan, I., & Simmons, C. P. (2018). Zika vaccines and therapeutics: landscape analysis and challenges ahead. BMC medicine, 16(1), 84.

[43] Sharp TM, Fischer M, Muñoz-Jordán JL, Paz-Bailey G, Staples JE, Gregory CJ, Waterman SH. Dengue and Zika Virus Diagnostic Testing for Patients with a Clinically Compatible Illness and Risk for Infection with Both Viruses. MMWR Recomm Rep. 2019 Jun 14;68(1):1-10. doi: 10.15585/mmwr.rr6801a1.

[44] Rodriguez-Morales AJ, Villamil-Gómez WE, Franco-Paredes C. The arboviral burden of disease caused by co-circulation and co-infection of dengue, chikungunya and Zika in the Americas. Travel Med Infect Dis. 2016 May-Jun;14(3):177-179.

[45] Villamil-Gómez WE, Mendoza-Guete A, Villalobos E, González-Arismendy E, Uribe-García AM, Castellanos JE, Rodríguez-Morales AJ. Diagnosis, management and follow-up of pregnant women with Zika virus infection: A preliminary report of the ZIKERNCOL cohort study on Sincelejo, Colombia. Travel Med Infect Dis. 2016 Mar-Apr;14(2):155-158.

[46] Arzuza-Ortega L, Polo A, Pérez-Tatis G, López-García H, Parra E, Pardo-Herrera LC, Rico-Turca AM, Villamil-Gómez W, Rodríguez-Morales AJ. Fatal Sickle Cell Disease and Zika Virus Infection in Girl from Colombia.Emerg Infect Dis 2016 May; 22(5):925-927.

[47] Villamil-Gomez WE, Sánchez-Herrera ÁR, Hernandez H, Hernández-Iriarte J, Díaz-Ricardo K, Castellanos J, de Jesús Villamil-Macareno W, Rodriguez-Morales AJ. Guillain-Barré syndrome during the Zika virus outbreak in Sucre, Colombia, 2016. Travel Med Infect Dis. 2017;16:62-63.

[48] Paniz-Mondolfi AE, Rodriguez-Morales AJ, Blohm G, Marquez M, Villamil-Gomez WE. ChikDenMaZika Syndrome: the challenge of diagnosing arboviral infections in the midst of concurrent epidemics. Ann Clin Microbiol Antimicrob. 2016 Jul 22; 15:42.

[49] Oduyebo T, Polen KD, Walke HT, Reagan-Steiner S, Lathrop E, Rabe IB, Kuhnert-Tallman WL, Martin SW, Walker AT, Gregory CJ, Ades EW, Carroll DS, Rivera M, Perez-Padilla J, Gould C, Nemhauser JB, Ben Beard C, Harcourt JL, Viens L, Johansson M, Ellington SR, Petersen E, Smith LA, Reichard J, Munoz-Jordan J, Beach MJ, Rose DA, Barzilay E, Noonan-Smith M, Jamieson DJ, Zaki SR, Petersen LR, Honein MA, Meaney-Delman D. Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure - United States (Including U.S. Territories), July 2017. MMWR Morb Mortal Wkly Rep. 2017 Jul 28;66(29):781-793. doi: 10.15585/mmwr.mm6629e1.