Zika Virus during the COVID-19 Pandemic: Epidemiological Parameters and Advances in Understanding the Infection

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Abstract

The COVID-19 pandemic has changed the focus of authorities and health organizations with respect to other infectious diseases. This review aims to examine the changes in global epidemiological parameters related to Zika virus during the COVID-19 pandemic and the progress made since 2020 in various aspects of infection. A narrative review was conducted, focusing on articles published between January 2020 and June 2023, covering epidemiology, pathogenicity, transmission, diagnosis, and treatment of Zika virus. The findings of this survey reveal that there has been a significant decrease in reported cases of Zika virus infection during the COVID-19 pandemic, however, advancements have been made in understanding the pathogenicity of the virus and the development of new diagnostic methods, vaccines, and treatments. The lessons learned from the response to COVID-19 have played a pivotal role in guiding efforts that have resulted in progress regarding various aspects related to Zika virus infection.

Keywords

ZIKV, Epidemiology, Infectious Diseases, Arboviruses

1. Introduction

The Zika virus (ZIKV) is a single-stranded flavivirus that belongs to the *Flavivi-*

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ridae family [1]. ZIKV was first detected in the Zika forest of Uganda in 1947 in mosquitoes of the species *Aedes* (*Stegomyia*) *africanus* and monkeys of the genus Rhesus [2].

Aedes aegypti and *Aedes albopictus* female mosquitoes are the main transmitters of ZIKV. Besides the transmission of ZIKV by mosquitoes, mother-to-child, sexual, transfusions, transplants, and laboratory accidents are less frequent modes of transmission [1].

ZIKV was first isolated from humans in Uganda and the United Republic of Tanzania in 1952 [3]. Since then, countries in Africa, America, Asia and the Pacific have reported shallow and sporadic outbreaks of ZIKV infection [3].

In 2007, about 75% of the population of the island of Yap (Federated States of Micronesia), combined with the outbreak of Zika virus in French Polynesia and other countries and territories in the Pacific, was the major ZIKV epidemic [3] [4]. In 2014 and 2015, Chile, Colombia, Suriname, Guatemala, El Salvador, Mexico, Paraguay, Venezuela, Panama and Brazil presented infections by ZIKV [5].

After the outbreak in Brazil in 2015, the Zika virus was considered a widespread pathogen capable of causing considerable sequelae [1].

The ZIKV disease is associated with Guillain-Barré syndrome in adults [3], and the congenital Zika Virus syndrome (SCZ), which causes abnormalities of the central nervous system, including microcephaly in neonates [4].

The major focus of health authorities and world organizations to cope with SARS-CoV-2 during the COVID-19 pandemic [6], leading to delays in notifications of probable cases and deaths caused by ZIKV was observed [7] [8]. However, the knowledge concerning the association of ZIKV with other diseases, forms of transmission, diagnosis, and treatment evolved because of the advances in coping with the COVID-19 pandemic. This development allowed to guide future efforts to control and prevent infection by ZIKV.

The COVID-19 pandemic demanded the attention of the scientific community. However, epidemiological studies for the implementation of control, prevention, and public health care measures must be maintained during concurrent virus outbreaks.

The present study intends to analyze the changes in the global epidemiological parameters related to ZIKV during the COVID-19 pandemic and the advances that have occurred since 2020 concerning some aspects of Zika virus infection.

2. Methods

A narrative review was used in this review. This is a research methodology structured around the selection of studies and the interpretation of information according to the subjectivity of the authors. It allows the acquisition and update of qualitative knowledge about a specific topic without the use of explicit and systematic criteria for the search and critical analysis of the literature.

The articles included in this narrative review were selected from January 2020

to June 2023 to provide relevant updates on the Zika virus scenario that occurred during the COVID-19 pandemic. For this purpose, we searched the keywords "Zika virus" and "pathogenicity," "epidemiology," "association with other diseases", "technologies", "diagnosis", "vaccines", "treatment" and "therapeutics" in reputable academic databases such as PubMed, Science Direct and Google Scholar.

3. Results

3.1. Epidemiology

The COVID-19 pandemic has emphasized the significance of global cooperation and preparedness to respond to disease outbreaks [9]. However, the swift and efficient sharing of scientific data and information on epidemiological parameters has not extended to other viral diseases.

According to the Pan American Health Organization (2023), after the first detection of the ZIKV in Brazil in March 2015, all countries and territories in the Americas confirmed local transmission, being Chile, Uruguay, and Canada the only exceptions [10]. However, there was a significant reduction in ZIKA transmission after 2016, particularly during the SARS-CoV-2 pandemic [10]. During this period, it is not possible to establish a direct correlation between the decrease in the number of ZIKV cases and the low infection rate.

Active circulation of the SARS-CoV-2 virus in countries and territories in the region of the Americas as of 2020 has led to a high demand for health services and epidemiological surveillance [10]. Epidemiological records indicate a total of 6012 cases of ZIKV during the first semester of 2021, a reduced number of cases than the same period of 2020 (13,624 cases, including 1 death reported in Brazil) [11]. The last epidemiological update reported 36,340 cases of ZIKA during the year 2022 [10] and according to PLISA (Health Information Platform for the Americas), 24,124 cases of ZIKV were reported up to July 2023 [12], showing that from 2022 epidemiological surveillance may have started to return to normality regarding the monitoring of arboviruses. The widespread administration of vaccines and booster doses against the SARS-CoV-2 virus reduced its transmissibility and gave way again to the monitoring of arboviruses that were neglected during the pandemic period.

Several countries in the African region have exhibited ZIKV transmission. However, there is a scarcity of information regarding the current incidence and transmission trends of the pathogen [13]. Since the last epidemiological update in 2022, Kenya has detected serological evidence of autochthonous transmission [13]. India (Kerala state) reported the first outbreak of ZIKV, initially detected in a pregnant woman in Trivandrum district [13]. Additionally, at least 70 cases of ZIKA have been confirmed from August 2021, from expanded testing within the community [13]. Countries in the Western Pacific Region, such as Malaysia and Singapore, have sporadically reported ZIKV infections, including a probable case of ZIKV-associated neonatal microcephaly [13].

The data presented on the current epidemiological scenario indicate that ZIKV was a major threat to public health during the coexistence with SARS-CoV-2. Many countries have outdated epidemiological parameters for arboviruses, representing a risk for possible endemic outbreaks. It is recommended that with the control of the SARS-CoV-2 pandemic, the governments update the epidemiological surveillance system for arboviruses in their respective countries.

3.2. Pathogenicity, Transmission and Association with Other Diseases

The scientific advancements made during the COVID-19 pandemic have provided discoveries related to the pathogenicity, transmission, and association of ZIKV with other diseases.

Research conducted during the COVID-19 pandemic found that ZIKV primarily affects neuronal precursor cells (NPCs) in the central nervous system (CNS) [14]. Polonio *et al.* (2022), demonstrated that fetal neuropathogenesis is related to the death of NPCs, glial inflammation, and subsequent tissue damage during ZIKV infection [14]. Furthermore, the overall gene expression of genes involved in neurodevelopmental, and the formation of neural circuits is regulated post-transcriptionally by miRNAs [14]. A correlation between miRNAs and target genes related to the antiviral immune response, cell death, and chemotaxis of immune cells, may contribute to the establishment of brain lesions [14]. Therefore, ZIKV replicates in NPCs that produce miRNAs, directly contributing to the pathogenesis of microcephaly fetal [14].

Glial cells are responsible for immune and inflammatory functions in the organism during virus infections [15]. ZIKV affects the adult nervous system by infecting glial cells present in the central nervous system (CNS) and peripheral nervous system (PNS), altering the physiological and pathological conditions of the individual [15]. Research performed at the beginning of the COVID-19 pandemic indicates that the pathogen induces glial dysfunction, representing a risk factor for neurodegenerative and neuropsychiatric diseases in adults [15]. Furthermore, ZIKV can reach the brain by replicating in the cells of olfactory unsheathing cells, causing alterations in the olfactory pathways that precede symptoms of neurodegenerative diseases [15].

Neurotrophic viruses, including ZIKV, are capable of infecting neurons that can damage the central nervous system and lead to Alzheimer's Disease (AD) [16]. However, the molecular mechanisms of ZIKV that underlie AD are still poorly understood [16]. Studies carried out during the SARs-CoV-2 pandemic showed that ZIKV infection in brain organoids can trigger pathological characteristics of AD, such as the expression of β-amyloid (Aβ) and phosphorylated Tau protein (p-Tau) in the cerebral cortex, which is responsible for progressive neurodegenerative diseases [16].

During the 2015 ZIKV outbreak, it was established that men shed viral RNA in their semen up to 6 months after symptomatic ZIKV infections [17]. To un-

derstand the mechanisms underlying ZIKV infection and persistence in the male genital tract, Vogt *et al.* (2022), demonstrated that prolonged release of ZIKV into semen during sexual activity is associated with inflammation of the male genital tract [17]. However, the authors assert that it is necessary to determine whether preexisting inflammation of the male genital tract induces prolonged seminal shedding of ZIKV or whether inflammation after infection with ZIKV leads to prolonged seminal shedding of ZIKV [17]. Furthermore, asserts that it is necessary to investigate whether treatment of male genital tract inflammation has the potential to reduce the viral spread of ZIKV through sexual transmission [17].

3.3. Zika Virus Diagnostic Technologies

Conventional methods available to diagnose ZIKV infection include neuroimaging diagnosis using magnetic resonance imaging (MRI) and computed tomography (CT), as well as viral isolation [18]. Furthermore, the World Health Organization (WHO) recommends the application of the molecular diagnosis for ZIKV using real-time quantitative polymerase chain reaction (RT-qPCR), serological tests such as ZIKV MAC-ELISA, and plaque reduction neutralization test (PRNT) [19]. However, there are limitations associated with the molecular methods mentioned, related to the requirement for a proper laboratory setup, expert technicians, and the high cost of reagents and equipment [18]. The serology of different flaviviruses, including ZIKV, is prone to false negatives due to extensive cross-reactivity between antibodies from previous infections or vaccination against other flaviviruses [20]. Therefore, there is a growing need for a rapid, inexpensive, and reliable detection approach for ZIKV.

The biosensors aiming at the rapid screening of SARS-CoV-2 during the pandemic have provided the foundation for new diagnostic technologies for ZIKV [21]. These devices are diagnostic tools constructed from nanomaterials that exhibit characteristics of high sensitivity, specificity, and practicality for the healthcare system [18]. In their operation, they use biological recognition elements, such as nucleic acids (genosensors), antibodies and antigens (immunosensors), and aptamers (aptasensors) [18]. Genosensors rely on the immobilization of DNA samples as the detection element [18]. Similarly, immunosensors exhibit selectivity and sensitivity based on the principle of antigen-antibody interaction [18]. Aptasensors are related to nucleic acid isolated from combinatorial oligonucleotides through an iterative in vitro amplification and selection process called systematic evolution of ligands by exponential enrichment (SELEX) [18]. These methods are promising for detecting ZIKV infections, which require proper testing for application in endemic areas and practical field situations.

3.4. Development of Vaccines and New Treatments against the Zika Virus

Currently, there are no specific vaccines or treatments available for Zika infec-

tions [22]. However, the existence of vaccines against various flaviviruses, such as the dengue virus (DENV) and the Japanese encephalitis virus (JEV), suggests the feasibility of developing a safe and effective vaccine against ZIKV [23]. Different platforms for vaccine development are in the preclinical and clinical trial stages [24]. These strategies include the production of DNA vaccines, mRNA, virus-like particles (VLPs), viral vectors, live attenuated virus, inactivated virus, peptide and protein-based vaccines, passive immunizations using monoclonal antibodies (MAbs), and vaccines targeting antigens derived from vectors [24] [25]. Experimental results by Lee *et al.* (2021) demonstrated that these vaccines induced specific humoral and cellular immune responses, as well as the reduction in viral RNA titers [25].

The platform of messenger RNA (mRNA) vaccines against SARS-CoV-2 is the first authorized biological preparation developed using this technology, representing promising alternatives to conventional vaccine approaches against ZIKV [25] [26]. The advantage of mRNA-based vaccines lies in their ability to be modified to enhance immunogenicity or eliminate unwanted side effects [25]. The mRNA vaccines developed during the COVID-19 pandemic as prophylactics for ZIKV infection include the candidate developed by Moderna (mRNA-1893, phase I trials registered at ClinicalTrials.gov, numbers NCT0406490), which is also being studied in phase II clinical trials (registered at ClinicalTrials.gov, numbers NCT04917861) in collaboration with the Biomedical Advanced Research and Development Authority (BARDA) [25].

There are no drugs approved by the Food and Drug Administration (FDA) available for ZIKV infection [26]. The repurposing of drugs to treat the disease was an approach widely used in the COVID-19 pandemic and has become an effective alternative in cases of emergency ZIKV outbreak [26]. Drugs that have anti-ZIKV activity evaluated by the year 2022 include sofosbuvir, suramin, chloroquine, mefloquine, amodiaquine, hydroxychloroquine, nitazoxanide, niclosamide, mycophenolic acid, ivermectin, and PHA-690509 [27]. The computational approach suggested that phytochemicals such as polydatin, liquiritin, cichoriin, dihydro genistin, and rapontin are economical approaches to inhibit ZIKV [26]. Muthuraj *et al.* (2023) explains that nutraceuticals such as curcumin, gossypol, and berberine have also shown potential antiviral effects against ZIKV [26].

4. Conclusions

The COVID-19 pandemic has changed the focus of authorities and health organizations with respect to other infectious diseases. Nonetheless, while significant attention has been directed towards COVID-19, notable progress has been made in comprehending the epidemiology, pathogenicity, transmission, diagnosis, and treatment of ZIKV.

During the COVID-19 pandemic, there was a substantial decrease in reported cases of ZIKV infection. It is crucial to acknowledge that numerous countries

still maintain outdated epidemiological parameters for arboviruses, posing a risk of potential endemic outbreaks. However, as the control of SARS-CoV-2 infection has been achieved, a return to normalcy in epidemiological surveys regarding ZIKV infection has been observed.

Studies conducted during the COVID-19 pandemic have provided valuable insights into more aspects of ZIKV pathogenicity, specifically its impact on neuronal cells, as well as confirming and reaffirming the persistence of the virus in the male genital tract.

In the field of diagnostics, the emergence of biosensors, inspired by the rapid screening tools employed for SARS-CoV-2, has demonstrated potential for the swift, cost-effective, and dependable detection of ZIKV infections.

While specific vaccines and treatments for ZIKV are currently unavailable, extensive research and development endeavors have been in progress. Several vaccine platforms, such as mRNA-based vaccines, have demonstrated promising outcomes in preclinical and clinical trials. Moreover, repurposing existing drugs and investigating the antiviral properties of natural compounds have offered potential options for ZIKV treatment.

The knowledge acquired from the response to COVID-19 has played a pivotal role in guiding endeavors that resulted in significant progress in several aspects of ZIKV infection. It remains imperative to uphold epidemiological studies, enhance surveillance systems, and sustain ongoing research and development for vaccines and treatments to effectively combat ZIKV.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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