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Chapter 5

Cocirculation and Coinfection Associated to Zika Virus in the Americas

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Abstract

Zika virus, a flavivirus, has arrived to Latin America in 2013. It became evident causing epidemics since 2015, first in Brazil and later in other countries in the region, such as Colombia, with a higher peak in 2016. The World Health Organization (WHO), based on cumulated evidence on its association with Guillain-Barre syndrome (GBS) and microcephaly and other birth defects (also the congenital Zika syndrome, CZS), declared for a period of almost a year, an international public health emergency. Epidemics in the region caused around 1 million cases with also additional complications beyond GBS and the CZS, which in patients with comorbidities lead to deaths. Among the events studied in the region, a number of cases with arboviral coinfections/codetection (dengue and chikungunya) were described and published beginning in Colombia and later in Brazil. In addition to that, cocirculation and still ongoing research on antibody-dependent enhancement (ADE) are challenges for physicians and public health authorities, given the implications for clinical manifestations and serological diagnosis in patients with previous exposition to other flaviviruses. We reviewed such aspects in this chapter.

Keywords: Zika, flavivirus, dengue, chikungunya, coinfection, cocirculation, arboviruses, epidemics, epidemiology

1. Introduction

Latin America and the Caribbean (LAC) have been threatened by an unprecedented explosion of emergent and reemerging arboviral epidemic outbreaks, such as the recent Zika virus

(ZIKV) and chikungunya virus (CHIKV) epidemics, but certainly in addition to previous endemoepidemic seasons of urban dengue (DENV) and sylvatic yellow fever (YFV). These emerging viral infections are largely due to a number of factors such as climate change, levels of urbanization, migration and tourism, commercial exchange activities, susceptible geographical areas (tropical and subtropical regions), as other, that have provided an ideal blend for vector availability and virus spreading among susceptible hosts. These have allowed a spillover of these pathogens from their naturally occurring niches and reservoirs to susceptible urban settings and newly unexposed geographic areas, showing how viruses are dynamic players in the ecology of the planet, particularly in tropical and subtropical areas [1, 2].

Figure 1. Conditions prone for arboviral *Aedes* vectors proliferation. Area endemic for Zika and other arboviruses cocirculation and coinfections, La Virginia Risaralda, Colombia.

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Arboviruses of medical importance (https://www.ncbi.nlm.nih.gov/Taxonomy/) are mostly included in the families Flaviviridae, Togaviridae, and Bunyaviridae. The Flaviviridae family includes dengue virus (DENV), yellow fever virus (YFV), Zika virus (ZIKV), and the Japanese encephalitis virus group (including the Japanese encephalitis virus, JEV, Usutu virus, USUV, and the West Nile virus WNV) [1–4]. The Togaviridae family includes chikungunya virus (CHIKV), Eastern equine encephalitis virus (EEEV), Mayaro virus (MAYV), Ross River virus (RRV), Sindbis virus (SINV), Venezuelan equine encephalitis virus (VEEV), and Western equine encephalitis virus (WEEV). Oropouche virus (OROV) belongs to the family Bunyaviridae [2, 3].

ZIKV shares multiple biological clinical similarities with other of those flaviviral and non-flaviviral arboviruses [1, 2]. The mosquito vectors *Aedes aegypti* and *Ae. albopictus* have facilitated these viruses' propagation; and have challenged the existing response capacities of local health systems. Many of the affected countries in Latin American countries were already facing existing challenges to build robust and reliable health systems [1, 4]. The presence of *Ae. aegypti* and *Ae. albopictus* is facilitated by socioeconomical and urban ecoepidemiological conditions, particularly the presence of old tires, where rain water is cumulated in poverty endemic areas (**Figure 1**).

In 2015, ZIKV emerged in LAC (although circulated apparently since 2013 in a silent pattern) as a leading public health priority, approximately 2 years after the CHIKV epidemic, leading to ZIKV, CHIKV, and DENV cocirculation, and the reporting of coinfections in different combinations. Although in the case of ZIKV infection, 80% of cases could be asymptomatic, clinical diagnosis of ZIKV, CHIKV, and DENV remains a challenge due to the considerable overlap in clinical presentations between them, and with other viral and nonviral infections [1, 4, 5], in addition also the problem of infection in patients with existing comorbidities that can lead to atypical, severe, and even fatal cases.

2. Cocirculation and coinfection of arboviruses

Currently, one of the major public health and biomedical challenges for the region is represented by cocirculation and coinfection of different flaviviral and nonflaviviral arboviruses [1, 5–9]. Their differentiation as their cross-reactivity between flaviviruses, particularly, implies immunological and diagnostic problems, when used serological tests [10–13].

The cocirculation of ZIKV, CHIKV, and DENV, in addition to other emerging and remerging pathogens (such as YFV, MAYV, OROV, among others), presents a number of challenges for clinical care and laboratory diagnosis in endemic areas [1, 13–21].

Patients infected with one or more of these viruses can present with similar clinical manifestations over a wide range of viremia, in some cases, suspecting that with coinfections, clinical symptoms of one of the infections can predominate while the other being asymptomatic [1, 22–24].

Clinical manifestations can initially guide the differential diagnosis and possibility of coinfection for the physicians, even in primary care, however, being challenging in multiple cases given the overlap of multiple symptoms (**Table 1**) [1].

This should be complemented with the epidemiological information of each case and epidemiology of cocirculating arboviruses, which is changing but available through multiple systems (e.g., WHO, Pan-American Health Organization [PAHO], ProMEDmail, RECOLZIKA). The broad range of possible viral and nonviral coinfecting agents and the nonspecific signs and symptoms at the initial stages of infection complicate even more the diagnostic approach to these cases, beyond the clinical aspects, implying as well the needs for the so-called multiplex diagnostic tools (specially molecular, those detecting RNA) to confirm a diagnosis of single infection or coinfection [1, 6, 7]. Recent field and clinical data have indicated that in nature, the people and mosquitoes may be infected by multiple arboviruses more frequently than has been previously appreciated, but still epidemiological studies need to approach in which proportion these occur during epidemics and nonepidemic seasons. In addition, exposure to multiple viruses tended not to affect mosquito susceptibility: mosquito midgut infection rates for each virus are similar whether the virus was delivered alone or in combination with another arbovirus [8, 11, 17]. Once a mosquito is infected, the virus disseminates through the mosquito body and replicates in the salivary gland before reaching the saliva to be transmitted [8]. In addition to this, there is no clear information yet on how is the viral interaction among infected cells, if they infected different cells, and how the immune cells in the human host as well in the mosquito interact when coinfections occur [8–15].

Clinical findings	**Main arboviruses**			
	CHIKV	**DENV**	**MAYV**	**ZIKV**
Fever	+++	++++	++++	++/0[a]
Myalgia/arthralgia	++++	+++	+++	++
Edema in limbs	0	0	0	++
Maculopapular rash	++	++	++	+++[b]
Retro-ocular pain	+	++	++	++
Conjunctivitis, nonpurulent	+	0	0	+++
Lymphadenopathies	++	++	+	+
Hepatomegaly	++	0	+	0
Leukopenia/thrombocytopenia	++	+++	++	0/+[c]
Hemorrhages	+	+++	0	0/+[c]

[a]Depends on geography and phylogeny of the virus, in some areas, patients do not have fever.
[b]Pruriginous (mild to severe).
[c]In some cases, these findings have been reported.

Table 1. Main clinical findings in CHIKV, DENV, MAYV, and ZIKV [1].

The ability of *Ae. aegypti* mosquitoes to be coinfected and cotransmit arboviruses could have important implications for the epidemiology, epidemics and syndemics (multiple simultaneous epidemics). The likelihood of coinfection by multiple *Ae. aegypti*-borne viruses may be increasing, especially during syndemics and high attack rates with multiple infected hosts. The first report of CHIKV and DENV coinfection occurred in 1964; those arboviruses were isolated from a single blood specimen taken from a patient in the acute phase of a dengue-like illness seen at Christian Medical College Hospital, Vellore, South India, in October that year [8]. The first cases of ZIKV coinfection and other arboviruses have already been reported: with DENV in New Caledonia in 2015 [9], which occurred in a traveler coinfected with ZIKV and DENV-3 and a local patient who was coinfected with ZIKV and DENV-1. In Colombia, during the beginning of ZIKV epidemics, a triple coinfection (the first globally reported), with DENV and CHIKV was reported in 2016 [10]. Also, in Colombia, in a pregnant woman, ZIKV with DENV and CHIKV was reported in the same year [11], in this case with a positive evolution.

When symptomatic infection with both ZIKV and DENV occurs, the clinical manifestations are apparently more severe [12]. However, it is not clear whether coinfection with multiple viruses could result in interspecific competition and interference during various stages of infection, or whether infection with one virus could enhance transmission of another, since our current understanding of coinfection and cotransmission by *Aedes* mosquitoes is limited [8].

Symptoms presented in reported cases of coinfections were severe arthralgia and joint swelling, nevertheless, the impact of coinfection of ZIKV and DENV on severity of illness in patients remains to be determined [12]. Recently, a study in Tolima, Colombia, following patients with post-CHIKV chronic inflammatory rheumatism (pCHIK-CIR), identified that in those patients with sequential (posterior) ZIKV infection, frequency of arthralgia and rheumatological persistent symptoms was higher [13]. The prevalence of arthralgia was higher in the group with Zika (50%) than the group without Zika post-CHIKV infection (33%). With further studies, it may be possible to prove if initial CHIKV infection is a risk factor for Zika virus disease, or if infection by other viruses after CHIKV increases likelihood of prolonging and/or intensifying the symptoms of the chronic phase. It cannot be ruled out that there are other cases of double or even triple coinfection (dengue, chikungunya, and Zika), as has been reported in Colombia in 2016 and it is also a key point to continue researching [13]. Even more, in such areas, during outbreaks, such as those occurred during 2015 for CHIKV and later for ZIKV in 2016, patients in countries such as Colombia were tested primarily for DENV, and just when negative tested for CHIKV, and if negative for DENV and CHIKV, then tested for ZIKV. This was the framework of the arboviruses sentinel network, which initially not allowed the detection of coinfections. Nevertheless, in the context of certain cases and research, clinicians were aware of infections with multiple pathogens in the differential diagnosis of dengue-like illness, especially in patients who returned from tropical and endemic areas [9–11, 14]. Coinfection diagnostic procedure could be improved by using multiplex RT-PCR, given the frequent cocirculation of multiple arboviruses in tropical regions [9–11, 14].

In Recife, northeast Brazil, the ZIKV and CHIKV coinfection has been associated with a severe case of meningoencephalitis associated with peripheral polyneuropathy in a 74-year-old patient [15], and a few cases of exanthematous illness associated with ZIKV, CHIKV, and DENV [16] also in Salvador, Bahía, Brazil have been reported. Although neurologic disturbances associated with several arboviruses were recognized, apparently there is a much higher frequency in neurological impairment following CHIKV and ZIKV infection than those resulting from DENV [15]. Nevertheless, as DENV is also neuropathogenic [17], multiple neurological consequences can occur during coinfections at this level, including central but also peripheral manifestations, including the Guillain-Barre syndrome, not only reported for ZIKV [18] but also for DENV [19] and CHIKV [20–22].

Some guidelines in USA and Brazil have been formulated to assist clinicians in assessing ZIKV in patients with DENV and CHIKV negative samples and in those who are negative on sequential testing for both pathogens. However, even if these guidelines are followed, coinfections may be missed [5, 11]. This complicates the diagnosis of patients with an acute febrile illness, as the spectra of clinical manifestations that result from infection with these viruses overlap significantly. Diagnosis is further complicated by cross-reactions observed in ZIKV-positive patients tested using immunoglobulin M (IgM) or nonstructural protein 1 (NS1) assays for DENV and vice versa and by limited data on the duration of anti-CHIKV immunoglobulin M positivity following acute infection. Molecular diagnostics can be used to detect and differentiate ZIKV, CHIKV, and DENV in the acute phase, and real-time reverse-transcription polymerase chain reaction (rRT-PCR) can provide quantitative data in addition to qualitative detection [6, 7, 23]. Where, these viruses cocirculate, especially in LAC, multiplex arbovirus detection including ZIKV, CHIKV, and DENV should be implemented for at-risk patients, including pregnant women, employing the same recommendations that have been issued for the screening of blood donors. A commercial multiplex molecular assay detecting ZIKV, CHIKV, and DENV has recently been accredited by the US Food and Drug Administration and may be used in routine practice [11]. In addition to these arboviruses, as mentioned, YFV, MAY, OROV as well different viral encephalitis viruses, should be also considered in this emerging scenario where is difficult to predict which of them will be the main arbovirus causing epidemics [24–26]. Given this complex scenario, any in public health and infectious diseases would be "paranoid" and trying to know who is the next one arbovirus that is knocking at our house door, wishing to be protected from its arrival, asking ourselves, "who can it be now?," as the title and lyrics of Collin Hay, in the 1981 pop song recorded by the Australian band "Men at Work." In our case, our fear and related anxiety is based on true facts that have been demonstrated by recent epidemics. Then and last, we need to increase our preparedness for emerging zoonotic and nonzoonotic arboviruses, their potential impacts and particularly to improve the vector control in tropical countries, as those in Latin America [24].

Till today, there are no single recommendations for management and treatment of such coinfections. Although that, general sense tends to recommend to orient the management to the control of the more severe of the infecting pathogens, e.g., DENV, but certainly not only acute, but also chronic implications of such coinfections (such as ZIKV and CHIKV), should be considered and followed up properly on time in order to mitigate on time their consequences [13, 27–36].

3. Cocirculation and coinfection of ZIKV with nonarboviral pathogens

Arbovirus coinfections are not the only coinfections reported. In some patients with other pathologies, an incidental diagnosis of ZIKV has been made. This situation is observed mainly in some tropical regions, where the requests for laboratory diagnosis of any arboviral infection (ZIKV, CHIKV, and DENV) in a hospitalized patient are systematically tested, as part of the public health surveillance scheme. Cocirculation of pathogens that cause acute febrile illness (AFI) complicates clinical diagnosis of patients, which can result in delays in initiating lifesaving medical interventions, as a fatal case of leptospirosis and ZIKV coinfection reported in Puerto Rico, in which ZIKV infection masked leptospirosis [37–39]. About malaria coinfection, it is described that a malaria infection may interfere with the specificity diagnosis laboratory for ZIKV, in that way, malaria may have led to false ZIKV-ELISA positives. However, the possibility of coinfection with malaria in endemic areas should be considered, tested, and treated [40, 41].

The broad symptomatic spectrum of some chronic diseases can mask the presences of other diseases, including infections. Therefore, it is important to describe the potential role played by sexually transmitted infections, mainly acute human immunodeficiency (HIV) infections, which usually debuts like fever and not specific rash which can be caused by a multitude of other pathogens, such as ZIKV, which can even be transmitted by sexual activity [42–45].

With the human immunodeficiency virus (HIV), there have been concerns about its implications. As HIV-infected adults with severe immunosuppression (e.g., a low CD4 cell count or an AIDS defining illness) experience more severe complications with infections in general, close clinical monitoring of Zika virus infection should be considered in these situations. More research is needed. Until now, there are only few case reports in the literature, but these have occurred mainly in patients under antiretroviral therapy (ARV), then with good levels of CD4 [43, 44, 46–52].

Finally, a very recent study in Colombia confirmed that coinfections would occur more than expected [53], among 157 patients in the Colombian-Venezuelan border, they found 7.6% with dengue and chikungunya, 6.4% with dengue and ZIKV, 5.1% with chikungunya and ZIKV and 1.9% with dengue, chikungunya, and Zika.

4. Conclusions

Diagnostic and treatment guidelines for those patients with simultaneous viral infections need to be urgently developed and tested in order to avoid delays in the diagnosis and associated mortality Rico [39]. The cocirculation of CHIKV, DENV, and ZIKV among existing ecological niches in LAC is a major public health challenge that requires efforts in understanding the transmission dynamics, the spectrum of clinical manifestations, health outcomes, and long-term sequelae of those coinfected with any of these emerging arboviruses [1, 11, 24]. The incidence and/or prevalence of coinfections is still a matter of concern for clinical reasons, but, its epidemiological assessment has not been furtherly studied even in the context of recent

epidemics. Efforts should focus on the necessity to contain the ongoing concurrent and future epidemics and to maintain strict and continued surveillance programs to monitor the spread of these viruses as well as the introduction of newly emergent pathogens [1, 8, 11]. In the field as well as in low-income and remote areas, clinicians should take into consideration the overlapping clinical features shared among these agents as well as the possibility of coinfection in their differential diagnosis. Hopefully, clinical tools, such as the use of the term "ChikDenMaZika syndrome" [1], will provide clinicians with a useful mnemonic tool that would aid in narrowing-down diagnosis when faced with arboviral-like disease symptoms such as fever, maculopapular rash, arthralgias, myalgias, and nonpurulent conjunctivitis (or conjunctival hyperemia). Such multiagent targeted approach in clinical diagnostics should also be extrapolated to the laboratory bench by improving the usage of multiplex RT-PCR diagnostic platforms for arboviruses in returning travelers, as well as residents of endemic areas, given the increasing reported frequency of cocirculation of multiple arboviruses and its emerging threat in tropical regions.

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