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EDITORIAL

The arboviral burden of disease caused by co-circulation and co-infection of dengue, chikungunya and Zika in the Americas

Viruses are dynamic players in the ecology of the planet. They inflict important suffering, disease, and death among human populations. In Latin America and the Caribbean (LAC), the concomitant co-circulation of dengue, chikungunya and Zika represents a major modern public health and biomedical challenge for the region, and potentially for some States in the United States. Several papers in this issue of Travel Medicine and Infectious Disease address the ongoing and ever increasing transmission of Zika virus [1,2]. Let us not forget dengue and chikungunya [3,4].

Prior to the arrival and subsequent spread of chikungunya and Zika viruses into human populations living in LAC, dengue has been the predominant arboviral infection in the region inflicting a substantial burden of disease [4]. Geographically, dengue is widely distributed throughout tropical and subtropical territories of the Western Hemisphere, from the State of Florida to Northern Argentina [3–5]. The mosquito vectors *Aedes aegypti* and *Ae. albopictus* have provided these viruses with wings; and have challenged the existing response capacities of local health systems, which together with viremic humans, are responsible for this rapid spread. Many of the affected countries in LAC were already facing existing challenges to build robust and reliable health systems. With the advent of the burden of disease associated to dengue, chikungunya and Zika viral infections, health systems have been overwhelmed and health system weaknesses in providing preventive and treatment services in a fair and equitable manner have been revealed. Furthermore, the epidemic nature of these outbreaks is transitioning to endemic levels of transmission influenced by multiple enabling drivers (poor socioeconomic conditions, climate change, migration, among others); or manifesting as periodic epidemics in the region and its countries.

In 2013, chikungunya emerged in LAC as a leading public health priority followed two years later, by the introduction of Zika virus [3,5]. Whilst these both emerging arboviral infection have deserved careful study, given its acute manifestations overwhelming existing healthcare institutions and due to potential long-term (even >6 years) sequelae in the case of CHIKV and probably in ZIKV including those associated with their potential for mother-to-child transmission [6], dengue is still by far the most with the highest incidence and the one with the highest case-fatality rate (Table 1). Even in 2015 in LAC, where all of these arboviruses were concomitantly circulating, more than four times reported cases of dengue were identified compared to the toll of chikungunya and Zika combined. Today, the number of patients affected by any of these arboviral diseases is sharply increasing since 2013, reaching over 3.5 million by the end of 2015. Nevertheless, ZIKV appeared in the Americas in the middle of 2015. By the end of May 2016, around 1,571,144 cases of dengue, chikungunya, or Zika have been confirmed. By extrapolation we can expect between 3 and 4 million cases by the end of 2016 (Table 1).

Historically, given the eco-epidemiological factors prevailing among tropical and subtropical settings in LAC [7], co-infection between two or more endemic tropical diseases (e.g. leptospirosis, malaria, acute Chagas disease, tuberculosis, measles, rickettsial or others) has been reported [8–10]. In this complex ecological and epidemiological setting, clinicians in affected areas are facing, on a daily basis, diagnostic dilemmas with patients presenting with acute febrile syndromes and exanthema (Table 2). This diagnostic challenge requires detailed clinical assessments and physical examinations to identify signs and symptoms (headache, retro-orbital pain, arthralgia, lumbalgia and conjunctivitis, among others) that may provide clinical clues to a probable diagnosis when no laboratory diagnosis can be performed (Table 2). Physical assessment is also of utmost importance in order to initially diagnose but also classify those patients requiring intensive medical care; or even for surveillance purposes. Patients with symptomatic Zika often present with exanthema (with pruritus), limb

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Table 1 Comparison of the number of cases of dengue, chikungunya and Zika in the region of the Americas, 2012–2016 (as of May 20, 2016). Source: PAHO.

Arboviral disease	2012	2013	2014	2015	2016	Total, 2012–2016
Dengue	1,398,876	2,712,632	1,515,824	2,888,330	1,146,590	9,662,252
Chikungunya	–[a]	111	1,147,515	726,478	114,199	1,988,303
Zika	–[a]	–[a]	–[a]	16,039	310,355	326,394
Total	1,398,876	2,712,743	2,663,339	3,630,847	1,571,144	11,976,949

[a] Not yet present and reported in the region.

Table 2 Comparison of known clinical findings, complications and long-term sequelae of dengue, chikungunya and Zika.

	Dengue	Chikungunya	Zika
Main Clinical Manifestations	Febrile exanthem Myalgias Arthralgias	Febrile exanthem Myalgias Arthralgias Rheumatism	Febrile exanthem (with pruritus) Conjunctivitis Arthralgias Edema in limbs
Main Complications	Hemorrhage Shock Fulminant hepatitis GBS Encephalitis Myositis Myelitis Mononeuropathies	Rheumatism GBS Retinitis Myocarditis	GBS Congenital microcephaly and other complications (CNS, ocular)
Long-term Sequelae	Neurocognitive deficits Paraparesis/Paraplegia (GBS and mononeuropathies)	Blindness? Paraparesis/Paraplegia (GBS) Dilated Cardiomyopathy (Myocarditis)? Chronic inflammatory rheumatism and arthritis Delayed neurocognitive development in children with congenital infection	Blindness? multiple ophthalmoological complications are reported (including macular, optical nerve and macular alterations) Neurocognitive development delay associated with microcephaly Paraparesis/Paraplegia (GBS)

edema, conjunctivitis, in addition to fever, myalgias, arthralgias and some with lymphadenopathy, usually without hepatomegaly (hepatomegaly is often seen in chikungunya), leukopenia and thrombocytopenia (seen more frequently in dengue and chikungunya) and bleeding (seen predominantly in dengue) (Table 2). Nevertheless, isolated cases with atypical manifestations are also being reported.

So far, despite the widespread co-circulation of these three arboviral infections, most patients tested simultaneously for these infections, are only diagnosed with only of them. In LAC, only limited reports of co-infection have been published. Clinical diagnosis is important but not enough to confirm a diagnosis of single infection or co-infection. Therefore, from a syndromic laboratory assessment approach, employing specific molecular-based techniques represents the optimal diagnostic approach along with standard cultures and serological tests. Nonetheless, individualized clinical assessments and laboratory testing should remain as the standard of care in all settings.

In summary, there is an urgent need to assess potential clinical spectrum of manifestations and of the overall epidemiological relevance of these potential arboviral co-infections. Diagnostic and treatment guidelines for those patients with simultaneous viral infections need to be urgently developed and tested. One of the most important concerns lies in understanding co-infection dynamics in terms of immunopathological consequences in the human host. In particular, it is unclear if previous arboviral infections, such as dengue and chikungunya represent a risk factor for atypical manifestations or severe Zika disease among affected populations. Another important consideration to be elucidated is the role of other comorbidities such as sickle cell anemia for either increased susceptibility to infection or severe disease, as it has already been suggested in recent reports. The co-circulation of these three arboviral pathogens among existing ecological niches in LAC is a major public health challenge that requires monumental efforts in understanding the transmission dynamics, the spectrum of clinical manifestations, health outcomes, and long-term sequelae of those co-infected with any of these emerging arboviruses. Further efforts are underway in Colombia and Brazil, among other countries in the region, to systematically collect these crucial data that will provide clues to better deal with these emerging arboviral infections.

Conflict of interest

There is no conflict of interest.

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