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Narrative review

Epidemiology of acute febrile illness in Latin America

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ABSTRACT

Background: The causes of acute febrile illness (AFI) in Latin America are diverse and their complexity increases as the proportion of fever due to malaria decreases, as malaria control measures and new pathogens emerge in the region. In this context, it is important to shed light on the gaps in the epidemiological characteristics and the geographic range for many AFI aetiologies.
Objectives: To review studies on community-acquired fever aetiology other than malaria in Latin America, and to highlight knowledge gaps and challenges needing further investigation.
Sources: PubMed from 2012 to April 2018.
Content: We found 17 eligible studies describing 13 539 patients. The median number of pathogens tested per individual was 3.5 (range 2–17). A causative pathogen could be determined for 6661 (49.2%) individuals. The most frequently reported pathogen during the study periods was dengue virus (DENV) (14 studies), followed by chikungunya virus (nine studies) and Zika virus (seven studies). Among the studies reporting concurrent infections, 296 individuals (2.2%) were found to have co-infections. In-hospital mortality was reported in eight (47%) studies, ranging between 0% and 18%.
Implications: DENV fever is the febrile illness most frequently reported, reflecting its importance, while chikungunya and zika viruses present increasing trends since their emergence in the region. Studies with systematic and harmonized approaches for detection of multiple pathogens are needed and would probably reveal a higher burden of neglected pathogens such as *Rickettsia* spp. and arenaviruses. The lack of point-of-care tests and harmonized approach limits the care provided by health professionals and the efficacy of surveillance for AFI in the region. **J. Moreira, Clin Microbiol Infect 2018;■:1**

Introduction

Fever is a common reason for seeking healthcare in Latin America associated with substantial morbidity and mortality [1]. A typical feature of many infectious and non-infectious diseases, the aetiological diagnosis of fever poses a considerable challenge for health professionals and surveillance systems, especially when confirmatory tests are not available at point-of-care [2]. Environmental conditions, socio-economic factors and availability of vaccines are some of the factors influencing the incidence and aetiology of infectious febrile illness in the region.

In tropical areas in the American continent (i.e. Amazon basin), the predominant cause of fever has historically been malaria; however, significant progress towards malaria control during the last decades has resulted in decreased incidence [3], along with a higher proportion of patients with acute febrile illness (AFI) that do not present malaria [4]. The progression from malaria to non-malaria febrile illness (NMFI) has shaped the fever epidemiology landscape and exposed new challenges for management and control in the region [5]. Hence, identifying the causes of NMFI is of paramount importance for improving patient care, for more efficient surveillance systems that include detection of emerging pathogens, and to guide implementation of diagnostic and preventive tools.

Arthropod-borne viruses, also known as arboviruses, represent one of the predominant aetiological agents responsible for human febrile illness in Latin America [6], where high temperatures, humidity and poor sanitation contribute to the proliferation of transmitting mosquitoes. Among these, dengue virus (DENV) has recently shown an expanding geographic range, moving from urban to rural areas, with efforts to control *Aedes aegypti* being largely unsuccessful [7]. The recent introduction into Latin America of zika

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virus (ZIKV) and chikungunya virus (CHIKV), which share many epidemiological and clinical features with DENV, highlights the lack of preparedness of local health systems to promptly and accurately ascertain the aetiology of AFI, resulting in inadequate management of and delayed responses to epidemics.

In this review, we summarize evidence about the aetiologies of community-acquired AFI in Latin America focusing on causes other than malaria, and highlight the important gaps in current knowledge that should be addressed to improve our understanding of AFI in the region.

Sources and selection criteria

We searched PubMed using medical subject headings and keywords such as 'non-malaria febrile illness', 'acute febrile illness', 'acute undifferentiated febrile illness' and other terms relevant to our review. For this report, we identified studies published in any language from 2012 to 1 April 2018. Reference lists of included studies were cross-checked to identify additional relevant studies. An additional search was performed in LILACS but did not reveal additional publications.

Eligibility criteria

We included observational studies enrolling individuals suffering from AFI in Latin America that were evaluated for at least two febrile diseases using laboratory-confirmed case definitions. For this review, Latin America was defined as the group of countries or territories that are situated south of the USA, thus including the Caribbean (see Fig. 1). We excluded studies conducted in other geographical areas; studies focused on a single aetiology of fever (e.g. outbreaks, seroepidemiology surveys; case reports/case series); studies of healthcare-associated infections, commentaries/editorials and those published before 2012. The complete search strategy is described in the Supplementary material (Appendix S1).

Study selection and data extraction

Two authors screened the title and abstracts. One author extracted the data, which were verified by a second author. The following variables were then extracted from each included paper and entered into a piloted extraction form: first author, year of publication, geographical location of the healthcare facility, study time dates and duration, study inclusion criteria, study size, age range, diagnostic techniques evaluated for each infection, timing of the sample collection, number of patients tested for each infection and those who were positive, co-infections, and in-hospital mortality rate.

The frequency of pathogens was recorded as zero if the study individually tested for them, but no pathogens were detected or when specific testing was not recorded. Next, we compared the frequency of pathogen isolation considering when the study was published. We categorized 2015 articles as the threshold, as after that CHIKV and ZIKV were introduced in the region.

Results

We found 17 eligible publications describing 13 539 patients [8–24]. Table 1 summarizes characteristics of the included studies. All except one study (in Spanish) were published in English. Ten (58.8%) were published before 2015 and seven (41%) from 2015 onwards. All studies were conducted between 2007 and 2016 and published between 2012 and 2018. Three (17.64%) were multicentre, and none included a healthy control group. The median number of pathogens sought in each study was 3.5 (range 2–17). The countries where the studies took place were mostly Colombia ($n = 4$), Brazil ($n = 4$) and Peru ($n = 2$), whereas studies conducted in the Caribbean were scarce. The study size ranged from 30 to 8996 participants, and the average duration of study enrolment was 11.35 (range:2–36) months. Seven (41.17%) were conducted for 1 year or longer. Each study site was mapped, and data related to study size were included (Fig. 1). Most studies enrolled febrile patients without age limits (91%) and were performed in urban settings (58.8%). Six (35.2%) studies were conducted in outpatient units, three (17.6%) in inpatient units, and seven (41.1%) evaluated both settings.

Of the 17 studies included, ten (58.8%) reported collection of paired acute-phase and convalescent-phase samples, whereas in seven (41.2%) only acute-phase was included. The inclusion criteria differed substantially between the studies, and a precise and harmonized definition of AFI was not provided.

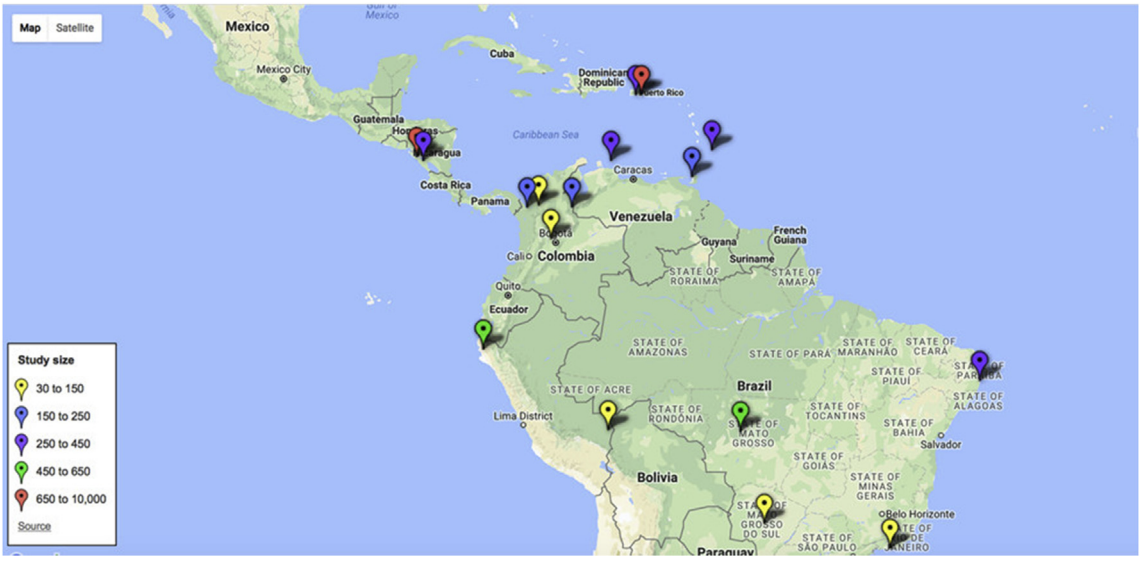

Fig. 1. Location of studies included in the review.

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