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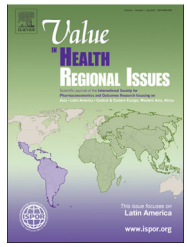

CLINICAL OUTCOMES STUDIES

Dengue Epidemiology and Burden of Disease in Latin America and the Caribbean: A Systematic Review of the Literature and Meta-Analysis

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ABSTRACT

Introduction: Dengue virus infection is the most common arthropod-borne disease worldwide with approximately 50 to 100 million cases of dengue infection occurring annually. Globally, dengue incidence has increased in the last 40 years, especially in Latin American and Caribbean (LAC) countries where the highest incidence is found. This systematic review aimed to present information on dengue disease burden and use of health resources in the LAC region in the last 15 years. **Methods:** We searched the main international and regional databases and generic and academic Internet search engines. Gray literature was retrieved mainly from regional health ministries and Pan American Health Organization. A set of inclusion criteria was defined. **Results:** We identified 2,041 articles of which 25 met these criteria, 13 for incidence and 12 for the use of resources and related costs. The pooled incidence of classic dengue fever was 72.1 cases per 100,000 persons-years in the 44 LAC countries analyzed (95% confidence interval 71.5–72.7), with an upward trend from 1995 up to 2010. Case-fatality ratio was highest in 1997 (0.12 [0.05–0.22]) and lowest in 2009, and the overall mortality was 0.02 per 100,000 people. More than 60% of the cases in the LAC region came from Brazil. The length of hospital stay ranged from 5 to 13 days. **Conclusions:** Activities to control dengue transmission in the region have been important but insufficient. The surveillance of dengue burden of disease and circulating strains help shape and evaluate the present and future health policies.

Keywords: dengue, disease burden, disease costs, epidemiology, Latin America, resource use.

Introduction

Dengue virus infection is transmitted primarily by *Aedes aegypti* and is the most common arthropod-borne disease worldwide. There are approximately 50 to 100 million cases of dengue infection annually. Roughly 2.5 billion people live in endemic areas that receive around 120 million travelers each year. The worldwide incidence of dengue and dengue hemorrhagic fever (DHF) has increased over the last 40 years with an expanding geographic distribution [1], especially in Latin America [2] The most important macro determinants responsible for this rise include increasing population density, poor sanitary conditions in urban areas, deterioration of public health systems, and lack of effective vector control programs in many countries. Globalization of the economy, international travel, and climatic changes might also play a role in the spread of the disease [3]. Four types of dengue virus have been identified up to date: DENV-1, DENV-2, DENV-3, and DENV-4 [4,5]. During the 1960s and early 1970s, dengue transmission was partially interrupted in the Americas because of an *Aedes aegypti* mosquito eradication campaign designed to prevent yellow fever [6]. Vector surveillance and vector control measures, however, were not continued and mosquito reinfestations occurred, causing outbreaks by DEN-2 and DEN-3 in the Caribbean, Central America, and South America [7]. In the late 70s and early 80s, DEN-1 and DEN-4 were introduced in some Latin American and Caribbean (LAC) countries, causing devastating epidemics [8]. Since then, the region has reported the highest incidence of cases worldwide (68% of all cases worldwide from 2000 to 2006), with periodic outbreaks every 3 to 5 years. The largest occurred in 2002, with more than 1 million reported cases [9–11]. The average incidence rate of dengue cases reported in these countries for the period 2000 to 2007 was 71.5 per 100,000 people annually, and increased in relation to the period 1990 to 1999. The average incidence rate of DHF was 1.7 per 100,000 for the period

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2000 to 2007, with 1391 deaths occurring in this period [9]. The direct and indirect costs of dengue illness and vector control programs represent a substantial economic burden on both the health sector and the overall economy of the region [10]. The high morbidity and mortality associated with this disease leads to a serious drain on the economies and the health systems of the affected countries; for example, a recent study reported a US $2.1 billion average cost due to the dengue epidemic in the Americas per year [11].

There are two approaches to the prevention and control of dengue and DHF: vaccines and vector control programs. Unfortunately, vaccines for these viruses are still under development, and vector control programs are costly and difficult to sustain. Also, there is little information regarding economic evaluations of dengue control programs in Latin America and the Caribbean.

To evaluate the cost-effectiveness of new treatment alternatives and the introduction of a vaccine in the region, it is crucial to count with estimates of the epidemiologic burden of the disease in LAC countries, taking into consideration incidence, morbidity and mortality, serotype circulation, and health resource impact. We conducted a systematic review on dengue disease burden and use of health resources in the LAC region for the period 1995 to 2010.

Methods

Search Strategy and Selection Criteria

We conducted a systematic literature review based on scientific literature from international and regional databases, generic and academic Internet search, and meta-search engines. Databases containing regional proceedings or congresses' annals and doctoral theses were searched. Web sites from main regional medical societies, experts, and related associations were consulted. An annotated search strategy for gray literature was included to retrieve information from relevant sources such as regional Ministries of Health, Pan American Health Organization (PAHO), and reports from hospitals.

The search was limited to CENTRAL (The Cochrane Library Issue 2010), MEDLINE, EMBASE, and LILACS (Latin American and Caribbean Health Science Literature) between January 1995 and November 2010. No language restriction was applied. The search strategy is detailed in Annex 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2013.10.002. The reference lists of articles finally included were manually searched for additional information. If data or data subsets of the same population were published in more than one source, the one with the largest sample size was chosen. Authors of relevant articles were contacted to obtain missing or extra information. Epidemiologic outcome meas ures included incidence, mortality, case-fatality ratio, hospitaliza tions, and patterns of circulation over time and serotype distribu tion over time. Economic outcomes included resource usage, indirect costs, and total costs of epidemics. Studies of any epidemio logical design, economic evaluations, and costing studies published were included, when at least 50 cases were evaluated with data collection from 1995 onwards. Dengue being a disease with man datory notification, all studies providing information at country level/province level supplemented the official countries' Ministries of Health databases (see Annex 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2013.10.002) and were thus included for meta-analyses, as long as no evidence of double counting of cases was detected.

Recently, the traditional World Health Organization dengue classification scheme (classic dengue fever, DHF, and dengue shock syndrome) was replaced with dengue without warning signs, dengue with warning signs, and severe dengue. We decided, however, to stick to the case definition and classification proposed by PAHO in its epidemiological bulletin because most PAHO data for the period of interest were reported in that way [12].

Review Methodology

Pairs of reviewers independently selected the articles on the basis of title and abstract according to prespecified criteria. During a second screening process, different pairs of reviewers independently categorized articles on the basis of retrieved full texts. Authors of articles were contacted when necessary to obtain missing or supplementary information. The risk of bias for observational studies was assessed through the Strengthening

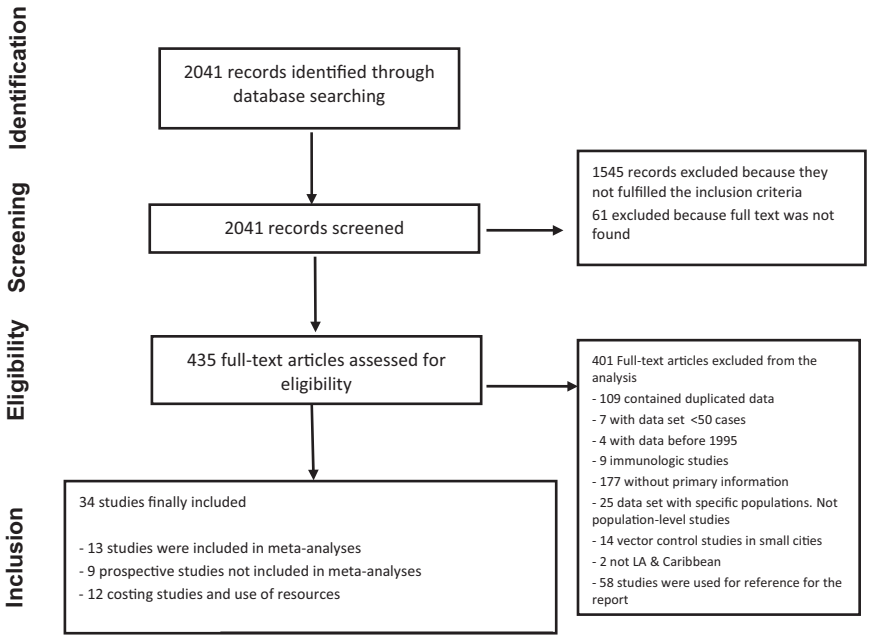

Fig. 1 – Study flowchart. LA, Latin American.