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Epidemiology of Malaria in Latin America and the Caribbean from 1990 to 2009: Systematic Review and Meta-Analysis

Ariel Bardach, MD, MSc, PhD[1,*], *Agustín Ciapponi, MD, MSc*[1], *Lucila Rey-Ares, MD, MSc(c)*[1], *Juan Ignacio Rojas, MD*[1], *Agustina Mazzoni, MD, MSc*[1], *Demián Glujovsky, MD, MSc(c)*[1], *Pilar Valanzasca, MD, MSc(c)*[1], *Marina Romano, MD*[1], *Natalia Elorriaga, BSc, MSc*[1], *María Julia Dantur Juri, MD*[2], *Marcos Boulos, MD, PhD*[3]

[1]*Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina;* [2]*Institute of Entomology "Dr. Abraham Willink," School of Medical Sciences, National University of Tucuman, Tucuman, Argentina;* [3]*Infectious Diseases Department, School of Medicine, University of São Paulo, São Paulo, Brazil*

ABSTRACT

Objective: The objective of this study was to evaluate the burden of malaria in Latin America and the Caribbean countries through a systematic review and meta-analysis of published literature, gray literature, and information from countries' public health authorities for the period 1990 to 2009. **Methods:** The random-effects meta-analysis of the prospective studies, carried out in very highly endemic areas, showed an annual incidence rate of 409.0 malaria episodes/1000 person-years (95% confidence interval [CI] 263.1–554.9), considering all ages, which was 40-fold the one estimated from areas with passive surveillance only. **Results:** Overall, the most prevalent species was *Plasmodium vivax* (77.5%; 95% CI 75.6–79.4) followed by *Plasmodium falciparum* (20.8%; 95% CI 19.0–22.6) and *Plasmodium malariae* (0.08%; 95% CI 0.07–0.010). Data from regional ministries of health yielded an estimated pooled crude annual mortality rate of 6 deaths/100,000 people, mainly associated with *P. falciparum*. **Conclusion:** This study represents the first systematic review of the burden of malaria in Latin America and the Caribbean, with data from 21 countries.

Keywords: epidemiology, incidence, Latin America, malaria, systematic reviews.

Introduction

It has been estimated that approximately 216 million malaria cases and 655,000 deaths due to malaria occurred in 2010 worldwide. Children from tropical developing countries are the most burdened group [1,2]. To date, there are five identified species of the malaria parasite causing malaria in humans (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*). *P. vivax and P. falciparum* are the most commonly described in Latin America and the Caribbean (LAC). *P. vivax* is prevalent in South and Central America, Middle East, and India and accounted for 77% of all malaria cases reported in 2011 in LAC. *P. falciparum* is the leading cause of death worldwide from a single infectious agent [2] and is predominantly found in tropical Africa, Southeast Asia, Oceania, Haiti, parts of the Amazon basin of South America, and the Dominican Republic. In fact, *P. falciparum* accounted for nearly all cases of malaria in Haiti and the Dominican Republic [3].

Malaria transmission has been reported in nearly all LAC countries, but it is highly variable across the LAC region and even within countries [4]. The risk of malaria transmission is increased in rural areas and fluctuates seasonally in many locations, with the highest transmission occurring at the end of the rainy season. Approximately 3 of every 10 persons living in LAC are at risk for malaria. In 2010, more than 675,000 cases were reported in 19 countries of the region [2]. A 2004 report from the World Health Organization estimated the global disease burden of malaria to be 46.5 million disability-adjusted life-years, 111,000 of which corresponded to LAC, representing approximately 0.2% of the global malaria burden [4,5]. Still, malaria constitutes a major public health problem in LAC's highest endemic areas. Currently, although there is information regarding the burden of malaria in the region [5], information regarding incidence, morbidity and mortality, parasite species distribution, admission, and case-fatality ratio (CFR) is scarce. Most available data come from public health organizations and ministries of health and have not been synthesized into a cohesive report.

The objective of this systematic review was to provide a comprehensive epidemiological analysis of the malaria disease burden in LAC.

Conflict of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

* *Address correspondence to*: Ariel Bardach, Institute for Clinical Effectiveness and Health Policy, Dr Emilio Ravignani 2024 (C1014CPV), Buenos Aires, Argentina.

E-mail: abardach@iecs.org.ar.

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Methods

Search Strategy

We conducted a systematic search including data from January 1990 to December 2009 using electronic databases included in Cochrane CENTRAL and specialized registers of the Cochrane Infectious Diseases Group, MEDLINE, EMBASE, and LILACS (see Web Appendix 1 in Supplemental Materials found at http://dx.doi.org.10.1016/j.vhri.2015.05.002). We also performed a search of Internet search engines (Scholar Google, Tripdatabase, Scirus) using keywords used for the electronic databases search. An annotated search strategy for nonindexed "gray literature" was used to obtain information from relevant sources for the same period, such as reports from regional ministries of health, the Pan American Health Organization (PAHO), the World Health Organization, institutional reports, special reports registered during outbreaks, databases containing regional proceedings or congresses' annals, reference lists of included studies, and consulting experts and associations related to the topic, according to a protocol based on the Meta-analysis Of Observational Studies in Epidemiology guidelines [6] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [7,8]. Authors from selected articles were contacted to obtain missing or additional information when it was needed.

Selection Criteria

We included data from control arms of randomized controlled trials and from observational studies, including cohort, case-control, surveillance, cross-sectional, and case-series studies from the LAC region. There were no language restrictions. Studies were included when at least 50 malaria cases were reported with patients of any age. Prospective studies were included irrespective of the number of cases or endemicity but were meta-analyzed if the follow-up was at least 6 months. We also included studies reporting congenital malaria (diagnosed by finding parasites in the neonate within 7 days of birth). Data regarding health resource consumption, such as length of hospitalization, use of supportive care, number of surgical and physician visits, school and work absenteeism, and reported direct costs per episode, were also explored. Studies with patients' enrolment before 1990, reviews, letters or health economic evaluations without original information, and studies not referring to LAC populations were excluded. We also excluded studies focusing only on vector epidemiology, antimalaric treatment and resistance, immunology, asymptomatic population (according to PAHO definition) [9], or malaria vaccines. A confirmed malaria case was defined as an individual with a positive light microscopy, a rapid diagnostic test, or other species elicitation technique (e.g., thin smear, immune fluorescence, polymerase chain reaction, enzyme-linked immunosorbent assay, and other molecular technologies). We planned separate analyses for gestational and congenital malaria. We applied the term "hyperendemic" to areas where transmission occurred throughout the year, at high intensity, and the disease burden was high in young children [10].

Data on incidence, mortality, and distribution of parasite species were obtained from PAHO and from official Ministry of Health databases available electronically for Mexico, Colombia, and Brazil [11–13]. The PAHO database did not include information from Cuba and Chile because these countries do not show malaria transmission [14]. If data were duplicated or data subsets appeared in more than one publication, the principal investigator was consulted and the study with larger sample size was used.

Outcome measures included incidence of malaria infection using the Annual Parasitic Index (calculated as the number of confirmed cases per population at moderate and high risk: 1–10 cases and >10 cases, respectively, per 1000 people per year) [15], hospitalization status, proportion of admissions attributable to malaria, mortality, CFR, slides analyzed, percentage of positive slides taken in health facilities, parasite species distribution, and patterns of circulation of *Plasmodium* species strains over time. We performed a meta-analysis of prospective studies that used active surveillance, reporting on incidence of malaria episodes.

Screening and Data Abstraction

Two reviewers independently prescreened all identified citations and selected studies, judging by title and abstract, that appeared to be eligible for the review. Two reviewers then independently evaluated full-text versions of all potentially eligible articles to evaluate whether they met inclusion criteria. Any discrepancies were resolved by consensus in both phases. Data were abstracted using a previously piloted electronic chart.

Assessment of Risk of Bias

Three reviewers (A.B., A.C., and D.G.) independently evaluated the quality of the methodology used in studies included in the systematic review. The risk of bias of observational studies was assessed by a modified checklist of essential items stated in Strengthening the Reporting of Observational Studies in Epidemiology and in Fowkes and Sanderson [16–20]. We used an algorithm (see Web Appendix 2 in Supplemental Materials found at http://dx.doi.org.10.1016/j.vhri.2015.05.002) to estimate a summary risk of bias considering six criteria (methods for selecting study participants, methods for measuring exposure and outcome variables, and methods to control confounding, design-specific sources of bias and comparability among groups, statistical methods, and declaration of conflict interests). Disagreements were solved by consensus.

Statistical Analyses

Information coming from prospective studies was not combined with official sources for meta-analysis and reported separately because of observed heterogeneity in methodologies and subject selection. To analyze our data, we conducted proportion meta-analyses. We applied an arcsine transformation to stabilize the variance of proportions (Freeman-Tukey variant of the arcsine square-root of transformed proportions method). The pooled proportion was calculated as the back-transformation of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed- and random-effects models. The estimates and their 95% confidence interval (CI) were calculated using the DerSimonian-Laird weights for the random-effects model, in which significant (>70%) heterogeneity between studies was found. We calculated the I^2 statistic as a measure of the proportion of the overall variation in the proportion that was attributable to between-study heterogeneity. Statsdirect version 2.7.9, Comprehensive Meta-analysis version 2.2.064, and STATA 9.0 were used for all analyses [21].

Results

The search strategy identified a total of 4472 citations from databases and 144 additional citations from the gray literature. After revision of title and abstracts and the removal of duplicates, 3655 unique citations could be used. Of these, 3277 references were excluded by title and abstract, 6 could not be retrieved in full text, and 372 studies were potentially eligible and assessed by full text (Fig. 1). A total of 64 studies were included; 24 reported malaria incidence or provided information to estimate it (Table 1)