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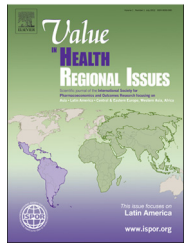

# Epidemiology of Malaria in Latin America and the Caribbean from 1990 to 2009: Systematic Review and Meta-Analysis

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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.

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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)

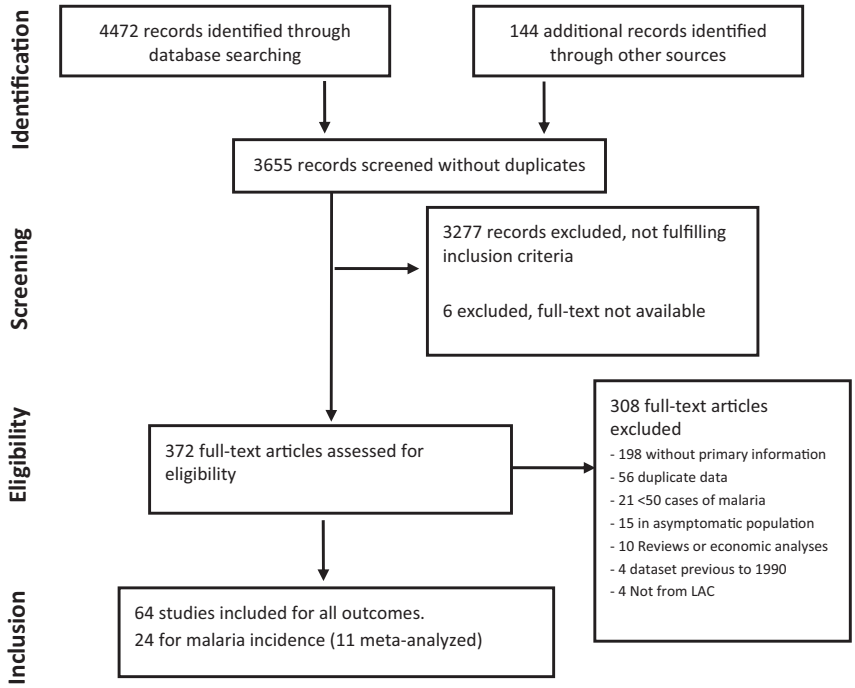


**Fig. 1 – Flow diagram of studies.**

[22–45], and the remaining 40 were useful for other outcomes such as species distribution, diagnostic methods used, hospitalizations, length of stay, and mortality (see Web Appendix 3 in Supplemental Materials found at 10.1016/j.vhri.2015.05.002). Of the 24 incidence studies, 11 were prospective with active case detection. Most of the data found came from Brazil, Colombia, Peru, and Ecuador. The main characteristics of the included studies and their methodological quality assessment are presented in a table in Supplemental Materials (see Web Appendix 4 in Supplemental Materials found at: http://dx.doi.org.10.1016/j.vhri.2015.05.002).

### *Incidence*

In those studies that presented data by age (all 24 incidence studies considered), children younger than 5 years had the highest rate, at 325.8 malaria episodes (95% CI 50.4–601.2) and adults (>14 years old) showed an incidence rate of 50.6 episodes/1000 person-years (95% CI 37.2–64.0) (Table 2). The random-effects meta-analysis of the prospective studies carried out in highly endemic areas showed an incidence rate of 409.0 malaria episodes/1000 person-years (95% CI 263.1–554.9), considering all ages (Table 2 and Fig. 2). The latter meta-analysis included 11 studies (13, counting substudies). Most areas meeting the definition of "highly endemic" [46] are located in the Amazon basin. The incidence of gestational malaria was 9.6 (8.3–10.9) cases/1000 pregnant women-year from the scarce studies identified in this subgroup of patients [38,47,48]. We did not find studies about the incidence of congenital malaria.

The meta-analysis of data reported by public health authorities in LAC (also referred to as official data) showed that the overall incidence rate for LAC in the study period was 10.4/1000 person-years (95% CI 10.3–10.6). This pooled figure includes areas of high, medium, and low risk, and countrywide population denominators, with all age groups considered. Fig. 3 shows a map with quintiles of incidence from the meta-analytic estimates from this official data. Suriname, French Guiana, and Guyana showed the highest malaria incidence, with rates exceeding 60 episodes/1000 person-years. Argentina, the Dominican Republic, El Salvador, Mexico, Panama, and Paraguay showed the lowest incidences, less than 1 episode/1000 person-years. An analysis of the yearly incidence (Fig. 4) showed a higher incidence during the time period 1993 to 2000, with the highest incidence of 22.6 episodes/1000 person-years (95% CI 21.5–23.6) in 1994 and the lowest of 5.7 (95% 5.1–6.2) in 2008. As expected, the $I^2$ statistic denoted a heterogeneity of greater than 80% in all analyses performed.

### *Slide Positivity Rate and Species Distribution*

Malaria slide positivity rate provides an alternative method for estimating temporal changes in malaria incidence, and it has been used in cross-sectional studies to define levels of endemicity. Our results show a downward trend over the study period (from 10% in 1990–1995 to <5% in 2007–2008). The overall positivity rate for the study period from identified studies was 8.6 (95% CI 7.7–9.7) (data not shown).

The proportion of malaria cases by parasite species and by country is presented in Table 3. Overall, the most prevalent species was *P. vivax* (77.5%; 95% CI 75.6–79.4) followed by *P. falciparum* (20.8%; 95% CI 19.0–22.6) and *P. malariae* (0.08%; 95% CI 0.07-0.010). *P. falciparum* appeared to be more frequent in the Dominican Republic, French Guiana, Haiti, and Suriname. In Guyana, the number of cases due to *P. vivax* and *P. falciparum* was similar, 47.8% and 50.4% of the cases, respectively (Table 3). Species distribution, reported diagnostic methods, and resource use outcomes by country can be found in Web Appendix 3 in Supplemental Materials.

### *Mortality and CFR*

The overall estimated malaria mortality rate from official sources was 6/100,000 person-years. These sources rely on passive surveillance from moderate-/high-risk areas. Suriname had the

**Table 1 – Malaria published studies reporting incidence by country, LAC 1990–2009.**

| Country | Location | Reference | Design | Setting* | Denominator | Age range (y) | Admission status | No. of cases of confirmed malaria | Incidence (malaria cases/1000 person-years)† | Starting/ ending date | Duration (mo) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bolivia | Amazon | [22] | Prospective cohort | Low | 622 p-y | >14 | | 72 | 116 | Mar-2003/ Sep-2003 | 7 |
| Brazil | Amazon, Rondhonia, Portuchelo | [23] | Cross-sectional | High | 157 | All | Outpatient | 53 | High | Jun-1994/ Jun-1995 | 13 |
| Brazil | San Pablo, Guaraparinga | [24] | Prospective cohort | Low | 522 | All | Outpatient | 106 | 192 | May-2000/Dec-2002 | 32 |
| Brazil | Acre, Granada | [25] | Prospective cohort | | 509 | All | | 195 | Medium | Mar-2004/ May-2005 | 14 |
| Brazil | Leonislandia, Peixoto Azevedo | [26] | Prospective cohort | Low | 187 | All | | 101 | 539 | Sep-1996/ Apr-1997 | 8 |
| Brazil | Amazon, Acre, Rio Branco | [27] | Cross-sectional | High | 38,470 | >14 | Inpatient | 445 | Medium | Jan-1996/ Dec-2001 | 72 |
| Brazil | Maranhão, San Luis, Paraiso | [28] | Cross-sectional | Low | 1,219 | All | Outpatient | 129 | 72 | Jan-1999/ Dec-2001 | 36 |
| Brazil | Rondônia, Urupá | [29] | Prospective cohort | Low | 840 | All | Outpatient | 655 | 780 | Jan-1991/ Dec-1996 | 12 |
| Brazil | Maranhã, São Luis, | [30] | Surveillance | Low | 217 | All | | 106 | 0 | | |
| Brazil | Acrelandia, Acre, Acre | [31] | Prospective cohort | High | 467 | All | Outpatient | 337 | 722 | Jan-2004/ Apr-2004 | 2 |
| Colombia | Choco, Quibdo | [32] | Cross-sectional | Low | 144,494 | All | Outpatient | 1053 | 3 | Mar-1997/ Jul-1997 | 4 |
| Colombia | Bogota | [33] | RCT | | 57 | 17–27 | | 19 | 333 | Jun-2000/ Jul-2000 | 1, 5 |
| Colombia | Nariño, La Tola | [34] | Prospective cohort | Low | 810 (721 p-y) | All | | 242 | 427 | Feb-1991/ Feb-1992 | 12 |
| Ecuador | Esmeralda, La Tola | [35] | RCT | Low | 232 (198 p-y) | 15–89 | | 46 | 233 | | 12 |
| Ecuador | Lower-Napo region | [36] | Surveillance | Low | 34,000 | All | Outpatient | 1258 | 9 | Jan-1992/ Dec-1995 | 48 |
| French Guiana | Camopi | [37] | Retrospective cohort | Low | 369 | <5 | | 676 | 935 | Jan-2001/ Dec-2001 | 12 |
| French Guyana | | [38] | Cross-sectional | High | 3,788 | All | Inpatient | 194 | Medium | Jan-1992/ Dec-1995 | 48 |
| Guatemala | Izabal, Izabal, Los Amates | [39] | RCT | Low | 341 | All | Outpatient | 70 | 200 | Sep-1990/ Aug-1991 | 12 |
| Haiti | | [40] | Cross-sectional | Low | 14,680 | All | Inpatient | 233 | 205 | Dec-1991/ Mar-1992 | |
| Honduras | La Mosquita, Bulnes, Palacios | [41] | Cross-sectional | Low | 115 | All | Outpatient | 34‡ | 16 | Jan-1999/ Mar-2000 | 5 |

*continued on next page*

**Table 1 – *continued***

| Country | Location | Reference | Design | Setting* | Denominator | Age range (y) | Admission status | No. of cases of confirmed malaria | Incidence (malaria cases/1000 person-years)† | Starting/ ending date | Duration (mo) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Peru | Grau, Sullana, Tambogrande, Bellavista | [42] | Surveillance | Low | 12,432 | All | Outpatient | 495 | 40 | Jul-1996/ Jun-1997 | 12 |
| Peru | Loreto | [43] | Case series | Low | 48,927 | 15–85 | Inpatient | 552 | | Jun-1996/ Jul-1997 | 13 |
| Peru | Loreto, Iquitos | [44] | Prospective cohort | Low | 1,400 | All | Outpatient | 1369 | 978 | Aug-1997/Jul-1998 | 11 |
| Venezuela | Estado Amazonas | [45] | RCT | | 495 (1045 p-y) | | | 196 | 187 | Jan-1999/ Dec-2000 | 24 |

LAC, Latin America and the Caribbean; p-y, person-years.
* Setting: High (reference health center) and Low (nonreference health center).
† Incidence rate as reported in the study regardless of the study design, or estimated by the information available in the article (episodes of malaria/1000 p-y). If not available, it was reported as high (>50 cases/1000 p-y) or medium (10–50 cases/1000 p-y).
‡ 115 total cases.

**Table 2 – Meta-analyzed estimates of the incidence of malaria episodes in published literature from highly endemic areas (1000 person-years).**

| Ages | Rate (95% CI) | Person-years |
|---|---|---|
| All ages (all study designs) | 202.9 (180.9–224.9) | 113,761 |
| 0–4 y | 325.8 (50.4–601.2) | 6,875 |
| 5–14 y | 177.4 (89.2–265.5) | 19,944 |
| >14 y | 50.6 (37.2–64.0) | 86,702 |
| All ages (only prospective studies with active case detection) | 409.0 (263.1–554.9) | 60,470 |
| All ages (only outpatient) | 104.0 (81.4–126.5) | 62,200 |

highest mortality rate followed by Guyana and French Guiana. Mexico and Argentina reported no deaths due to malaria in the years considered (Table 4). The pooled mortality estimate from identified prospective studies [43,44] done in highly endemic areas was 65.8/100,000 person-years (95% CI 43.4–88.2). Table 5 presents pooled mortality estimates by year for the whole region.

The highest CFR was reported in the Dominican Republic, with 0.6% (95% CI 0.48–0.73). In the remaining countries, the CFR was lower than 0.1% (data not shown). Because of the scarcity of information on the use of health resources in the management of malaria cases, a meta-analysis was not performed. Four studies [26,43,49,50] reported a median length of stay of 4 days (range 3.3–6.0 days).

### *Malaria Epidemiology in Brazil*

Brazil has complete, online public information about malaria hospitalizations, mortality, and incidence by age [13]. Data from this source pertaining to the same period were analyzed and shown separately. Malaria incidence from Brazilian studies done in endemic areas in children younger than 5 years was 40 episodes/1000 person-years (95% CI 0–104.0). In persons older than 14 years, the rate was 292.9 episodes/1000 person-years (95% CI 124.8–461.1). Analysis of official Brazilian public health system online database (DataSUS) data on the incidence rates across regions showed heterogeneity, with high incidence rates in the Northern Region, including the states of Acre, Amapá, Amazonas, Pará, Rondônia, Roraima, and Tocantins (35 episodes/1000 population), and lower rates in the Central West Region, including the states of Goiás, Mato Grosso, Mato Grosso do Sul, and Distrito Federal (5 episodes/1000 population), and rates less than 1 episode/1000 persons in the remaining regions. The pooled incidence rate of hospitalizations was 34.7 /1000 population per year regardless of age (95% CI 28.45–40.96). *P. vivax* accounted for 35.4% of all malaria hospitalizations (95% CI 30.4–40.52).

Information on incidence by hospitalization status, proportion of malaria admissions out of the total, slides analyzed, percentage of slides taken in health facilities that tested positive, parasite species distribution, and patterns of circulation of *Plasmodium* species strains over time is not shown, but available on demand.

## Discussion

This study represents the first systematic review and meta-analysis of malaria burden in LAC, synthesizing data from prospective studies and official data from 21 countries. We found an estimated pooled incidence of 409.0 malaria edpisodes/1000 person-years from prospective studies and 10.4/1000 person-years estimated from official sources. The pooled incidence reported by prospective studies is 40-fold that calculated on the

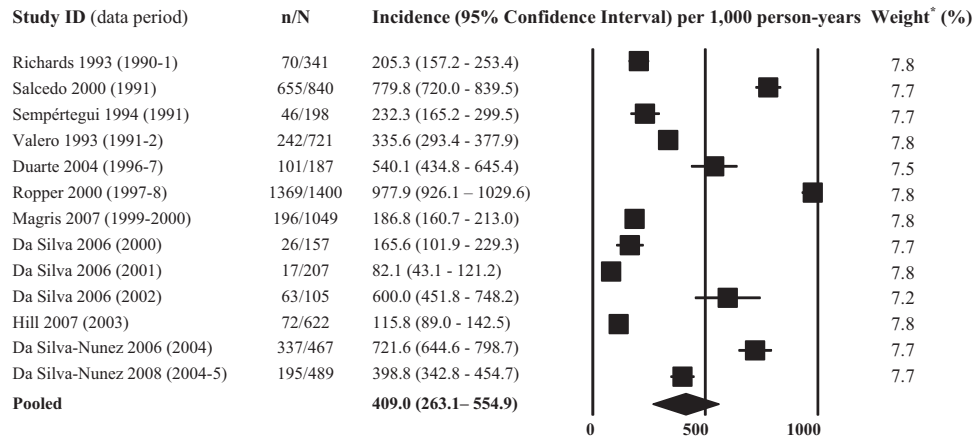


**Fig. 2 – Malaria incidence in highly endemic areas (1990–2009). Prospective studies with active case detection meta-analysis. *From random-effects meta-analysis.**

basis of cases reported by ministries of health, depicting the difficulty of drawing adequate estimates of the real disease burden.

The most likely reason for this huge difference is that most prospective studies were carried out in highly endemic areas in the context of active case detection, whereas official information is derived from areas of moderate or high risk for a given country or region, mostly coming from passive surveillance and much more prone to underreporting of cases. For example, Unified Health System (SUS, Sistema Único de Saúde) data in Brazil show that in most endemic areas such as Acre or Roraima, the Annual Parasitic Index registered for 2010 was less than 50 cases/1000 persons [13], still much lower than the pooled estimate from studies in regions with active detection. Indeed, the World Malaria Report 2011 highlights the presence of severe underreporting of cases in many continents [2].

In addition, it is important to consider that most of the published studies identified were relatively old. Pooled figures of incidence, species distribution, or mortality from meta-analyses help in making meaningful comparisons with other geographical regions and over time [2]. The upper and lower bounds of summary estimates probably represent with the least uncertainty the range within which the true estimate lies. Other malaria meta-analyses that reported incidence or prevalence as pooled estimates have been published, [51,52] and endemicity maps for LAC exist. [53,54] PAHO online data also show that the incidence and the Annual Parasitic Indexes vary widely over time and space. The present work, however, adds relevant information as age distribution.

Brazil accounted for most of the cases in the region followed by Colombia, Peru, and Venezuela, highlighting the higher burden of cases in the Amazon rainforest (shared by Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Peru, Suriname, and Venezuela). There were an estimated 216 million episodes of malaria worldwide in 2010, of which approximately 81% were in the African Region, mostly due to *P. falciparum* [2]. In LAC, however, the most common parasite species was *P. vivax*, accounting for 77% of the cases in most of the countries, except in the Dominican Republic, Colombia, French Guiana, Guyana, Haiti, and Suriname.

Our estimated mortality was considerably lower in LAC at 6/100,000 person-years compared with that in Africa, where it was estimated to be 84.3/100,000 person-years in 2010 [2] and consistent with Murray et al.'s [1] analyses regarding the relatively very small contribution of LAC deaths to the global mortality burden of disease. An estimated 86% of the deaths by malaria in the world occur in children younger than 5 years. Africa is disproportionately affected, with 91% of the deaths occurring in those younger than 5 years, compared with 29% in the Americas [2].

In the Americas, mortality decreased by 55% between 2000 and 2010, probably because of the impact of disease control programs [2]. The peak number of malaria cases in the region was reported in 1994, with approximately 1.3 million cases registered. After 1998, the total number of cases continued declining, with the lowest values of 7/1000 persons-years at risk in 2010, reflecting the effectiveness of the regional Roll Back Malaria Initiative [2]. Because the global malaria control strategy was adopted in 1992, the 21 LAC countries with varying degrees of active malaria transmission implemented three control strategies in their national programs: 1) early diagnosis and prompt treatment; 2) planning and implementation of selective and sustainable preventive measures, including vector control and insecticide-treated bednets; and 3) early detection, containment, and prevention of epidemics. In addition, local capacities in basic and applied research were strengthened to permit and promote the regular assessment of a country's malaria situation, particularly the ecological, social, and economic determinants [55]. These strategies might explain the decrease in cases observed in the last decade (Fig. 4).

Most of the cases occurred in restricted areas, and were often related with activities such as mining, hydroelectric dam building, or wood extraction, for which specific and effective control programs are needed. The naive, nonimmune individuals, mostly working men with their bodies exposed to mosquito bites, are usually the population most affected (due to the hot and humid weather, and men working full time). In addition, in the last decade, there was a sharp increase in laboratory access in the Amazon region, with consequent decrease in the time to diagnosis and treatment of the disease. In the past, the confirmation of the malaria diagnosis by blood slides was done mainly for highly suspicious cases, leading to a relatively high percentage of positive blood slides. It is possible that in more recent years, improvements in the availability and access of malaria diagnostic tests performed for people with much lower likelihood of having malaria could have resulted in a much lower slide positivity rate. PAHO databases hold detailed country-specific epidemiologic information on malaria, for the last 20 years [56].

The availability and adoption of artemisinin combination therapies by national malaria control programs to treat *P. falciparum* malaria in the last decade in most LAC countries also led to the decrease in malaria deaths. The smaller number of deaths reported by the Global Malaria program could also be

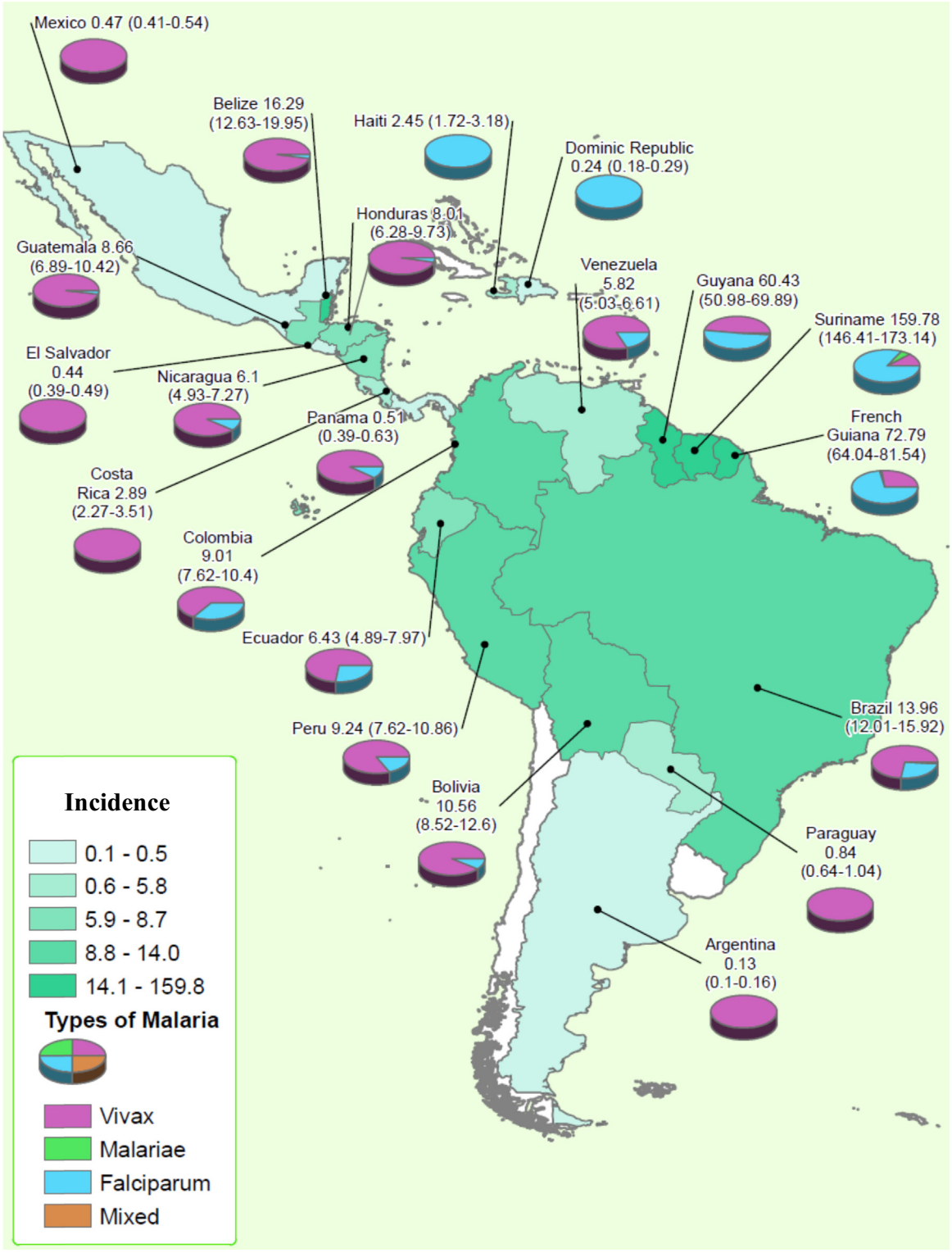


**Fig. 3 – Population-wide pooled incidence quintiles by country (per 1000 person-years) and species distribution (official Ministry of Health data, 1990–2009). This map does not reflect endemic areas within a country, but rather officially registered cases relating to the country's total population for the years considered.**

explained in part by the larger number of *P. vivax* malaria cases found in our meta-analysis. *P. vivax* causes a more clinically benign form of malaria, leading to a lower mortality rate than in regions where *P. falciparum* predominates. It can cause complicated and severe disease, however, as per clinical criteria (thrombocytopenia, bleeding, and other symptoms) in particular populations such as in pregnant women, and severe cases have been reported in LAC [57–61]. *P. vivax* thus carries a high burden of disease in terms of morbidity in LAC according to our pooled estimates. Underreporting of deaths to the health system may

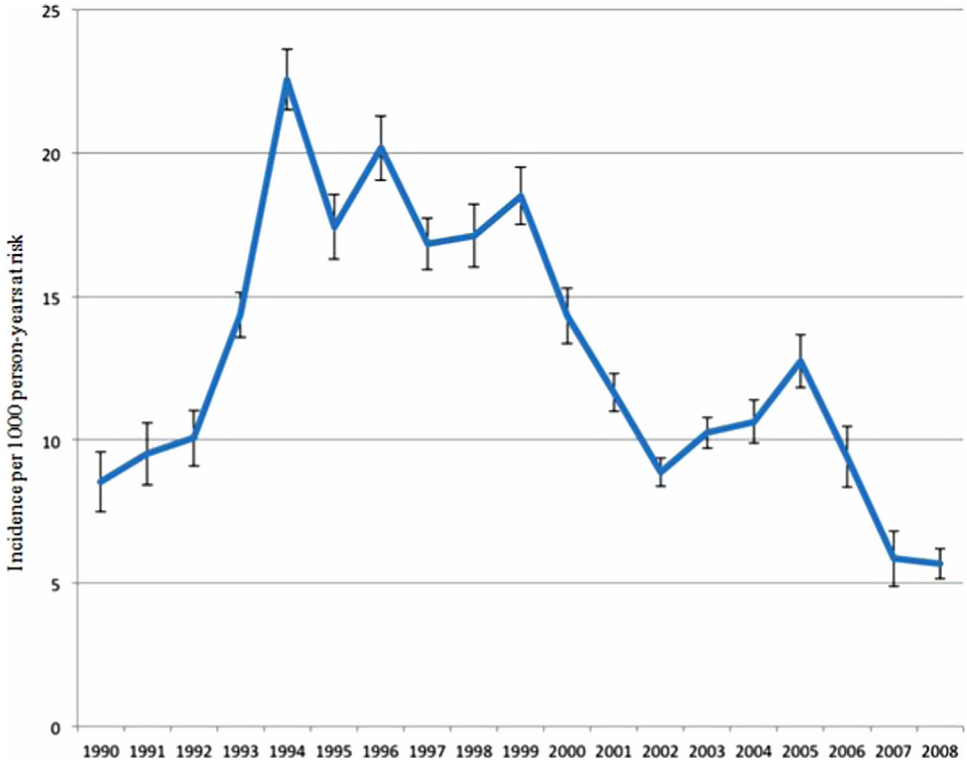


**Fig. 4 – Pooled incidence from endemic areas (API) in Latin America and Caribbean, from official sources (1990–2008). Spikes denote 95% confidence intervals. API, Annual Parasitic Index, calculated as the number of confirmed cases per population at moderate and high risk, per 1000 person-years.**

also result in lower mortality rates. It is unlikely that the control of *P. vivax* is possible until an effective vaccine is available, particularly because of the toxic profile of the currently available antirelapsing drugs.

The present systematic review and meta-analysis provides valuable information regarding malaria burden from official reports and articles published in peer-reviewed journals in LAC, particularly on incidence, information that is not available from

**Table 3 – Pooled percentage (%) of malaria parasites species by country (1990–2008) from MoH official data.**

| Country | *P. vivax* | *P. malariae* | *P. falciparum* | Mixed |
|---|---|---|---|---|
| Argentina | 99.88 (99.8–99.94) | 0.04 (0.01–0.08) | 0.12 (0.06–0.2) | |
| Belize | 97.41 (95.91–98.57) | 0.04 (0.01–0.08) | 2.54 (1.38–4.04) | |
| Bolivia | 91.48 (89.44–93.31) | 0 (0–0) | 8.24 (6.49–10.17) | 0.39 (0.23–0.6) |
| Brazil | 72.61 (68.52–76.51) | 0.08 (0.05–0.13) | 26.69 (22.63–30.96) | 1.06 (0.87–1.26) |
| Colombia | 62.72 (59.82–65.58) | 0.03 (0.01–0.05) | 36.46 (33.71–39.25) | 0.72 (0.45–1.05) |
| Costa Rica | 99.42 (98.95–99.75) | 0.01 (0–0.02) | 0.44 (0.28–0.63) | 0.18 (0.09–1.3) |
| The Dominican Republic | 0.38 (0.23–0.57) | 0.02 (0–0.03) | 99.61 (99.42–99.77) | 0.01 (0–0.04) |
| Ecuador | 72.59 (66.63–78.18) | 0 (0–0) | 27.41 (21.82–33.37) | |
| El Salvador | 99.67 (99.52–99.79) | 0.01 (0–0.02) | 0.32 (0.2–0.46) | |
| French Guiana | 26.94 (19.76–34.79) | 1.39 (0.67–2.35) | 70.53 (62.81–77.69) | 0.88 (0.65–1.14) |
| Guatemala | 97.32 (96.84–97.76) | 0.01 (0–0.02) | 2.58 (2.14–3.05) | 0.09 (0.03–0.17) |
| Guyana | 47.82 (45.34–50.31) | 0.03 (0–0.09) | 50.43 (47.4–53.45) | 1.27 (0.71–1.97) |
| Haiti | 0 (0–0.01) | 0 (0–0) | 100 (99.99–100) | |
| Honduras | 96.90 (96.13–97.58) | 0 (0–0) | 3.01 (2.36–3.74) | 0.17 (0.11–0.24) |
| Mexico | 99.28 (99.02–99.5) | 0 (0–0) | 0.79 (0.55–1.06) | |
| Nicaragua | 91.52 (89.92–92.99) | 0 (0–0) | 8.48 (7.01–10.08) | |
| Panama | 90.90 (87.34–93.91) | 0.01 (0–0.03) | 9.08 (6.07–12.63) | 0.04 (0.02–0.06) |
| Paraguay | 99.49 (99.11–99.76) | 0.01 (0–0.03) | 0.47 (0.21–0.83) | 0.02 (0.01–0.05) |
| Peru | 83.65 (78.59–88.15) | 0.02 (0.01–0.03) | 16.28 (11.78–21.36) | |
| Suriname | 9.99 (7.46–12.85) | 5.25 (3.57–7.23) | 83.53 (78.94–87.65) | 0.59 (0.42–0.8) |
| Venezuela | 81.73 (79.47–83.88) | 0.09 (0.06–0.14) | 17.75 (15.53–20.09) | 0.59 (0.35–0.88) |

MoH, Ministry of Health.

**Table 4 – Pooled estimates of malaria mortality in Latin America and Caribbean by country, 1990–2009, from official MoH sources (per 1000 person-years).**

| Country | Rate (95% CI) | Person-years |
|---|---|---|
| Argentina | 0 (0–0) | 39,189,880 |
| Belize | 0.22 (0.05–0.4) | 2,922,949 |
| Bolivia | 0.15 (0.08–0.21) | 41,815,394 |
| Brazil | 0.32 (0.26–0.39) | 788,433,774 |
| Colombia | 0.24 (0.18–0.31) | 201,192,440 |
| Costa Rica | 0.04 (0.01–0.07) | 19,462,989 |
| The Dominican Republic | 0.13 (0.09–0.16) | 135,179,325 |
| Ecuador | 0.01 (0–0.02) | 98,006,425 |
| El Salvador | 0.01 (0–0.02) | 60,285,129 |
| French Guiana | 1.15 (0.43–1.87) | 1,560,447 |
| Guatemala | 0.12 (0.05–0.19) | 57,024,289 |
| Guyana | 2.19 (1.31–3.07) | 5,702,374 |
| Haiti | 0.45 (0.29–0.61) | 68,307,551 |
| Honduras | 0.01 (0–0.02) | 64,372,819 |
| Mexico | 0 (0–0) | 485,925,763 |
| Nicaragua | 0.18 (0.12–0.23) | 80,169,956 |
| Panama | 0.03 (0.01–0.04) | 52,479,404 |
| Paraguay | 0.02 (0–0.04) | 31,974,670 |
| Peru | 0.22 (0.15–0.29) | 147,601,049 |
| Suriname | 7.13 (4.56–9.69) | 1,599,778 |
| Venezuela | 0.27 (0.19–0.34) | 112,942,818 |
| All LAC | 0.06 (0.06–0.07) | 2,496,149,223 |

CI, confidence interval; LAC, Latin America and Caribbean; MoH, Ministry of Health.

PAHO databases. It is possible but unlikely that relevant studies were omitted. The inclusion of official and published data allows a more complete picture of the burden of disease in LAC, including incidence and mortality, than by using official data only. Our study also describes the most common malaria parasite species in LAC, mortality, CFR, and hospitalization, which was previously missing in official data sources and highly relevant when considering health resource utilization as well as the implementation and evaluation of malaria control programs [62].

The main limitations of this review include the high risk of bias of many of the included incidence studies, mainly due to selection bias; the lack of population-based and well-designed epidemiological studies; and the important degree of heterogeneity evidenced in the information retrieved regarding designs and objectives of the different studies. Data on incidence, however, were meta-analyzed only in the case of prospective, active case detection high-quality studies, and random-effects models were selected. Because these prospective studies were done mainly in high transmission areas, their estimates are inconsistent with those coming from official Ministry of Health data, which may be pertinent to broader geographic areas. Summary epidemiologic information from highly endemic areas is meaningful to accurately determine the burden of the disease, in order to improve control programs. Another shortcoming detected was the paucity of information on mortality rates and age distribution of cases caused by *Plasmodium* species.

Considerable changes have taken place in the region, politically and socioeconomically, both very important for health and health care. National and international awareness of the malaria problem has increased in the period analyzed and control programs were undertaken and fortunately, progress has been made, especially since 2005. Updating global maps of malaria endemicity is a priority because it enables a better-informed resource allocation. Future research is needed to assess the economic and social impact of malaria, and to supply detailed information, regarding incidence, prevalence, costs, work absence, and social burden of malaria, that will improve our knowledge and management of the disease.

In conclusion, although this study shows a decrease in the number of cases and deaths during the last decade and a decrease in the incidence of disease caused by *P. falciparum*, malaria remains an important health problem in LAC.

**Table 5 – Malaria mortality in LAC by year (100,000 persons/y).**

| Year | Rate (95% CI)* | No. of countries | Total person-years |
|---|---|---|---|
| 1990 | 0.19 (0.11–0.27) | 15 | 113,585,835 |
| 1991 | 0.24 (0.16–0.32) | 16 | 81,668,005 |
| 1992 | 0.13 (0.05–0.22) | 10 | 41,962,276 |
| 1993 | 0.04 (0.00–0.17) | 3 | 7,475,912 |
| 1994 | 0.11 (0.03–0.19) | 5 | 25,541,752 |
| 1995 | 0.16 (0.02–0.3) | 6 | 33,879,939 |
| 1996 | 0.26 (0.13–0.39) | 8 | 78,616,582 |
| 1997 | 0.33 (0.12–0.54) | 6 | 24,145,408 |
| 1998 | 0.12 (0.07–0.17) | 17 | 196,084,569 |
| 1999 | 0.13 (0.08–0.18) | 17 | 173,352,256 |
| 2000 | 0.10 (0.06–0.14) | 18 | 204,943,289 |
| 2001 | 0.09 (0.06–0.12) | 20 | 210,429,863 |
| 2002 | 0.09 (0.06–0.12) | 20 | 181,035,762 |
| 2003 | 0.07 (0.04–0.09) | 19 | 307,081,045 |
| 2004 | 0.06 (0.03–0.08) | 20 | 247,555,957 |
| 2005 | 0.08 (0.05–0.11) | 20 | 256,019,124 |
| 2006 | 0.09 (0.05–0.13) | 20 | 101,340,883 |
| 2007 | 0.1 (0.06–0.14) | 20 | 120,927,375 |
| 2008 | 0.05 (0.02–0.08) | 18 | 90,503,391 |

* CI, confidence interval; LAC, Latin America and Caribbean.

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## Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.vhri.2015.05.002 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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