Malaria Mortality in Venezuela: Focus on Deaths due to *Plasmodium vivax* in Children*

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Summary

Morbidity and mortality burden of malaria in the childhood represents a public health threat not only in countries with high levels of transmission, but also in those, such as Venezuela and others in Latin America, with moderate to low transmission. Usually its mortality has been attributed just to *Plasmodium falciparum* malaria, but the changing patterns of increase in *Plasmodium vivax* malaria morbidity and mortality are now causing concern. We studied malaria mortality by analyzing different epidemiological variables during a 10-year period in Venezuela, finding mortality rates ranging 0.10–0.36 deaths/100 000 population, with almost a third of deaths in children (<10 years old), corresponding 270 deaths to *P. falciparum* cases and 30 to *P. vivax*; but along the period with a decrease trend for *P. falciparum* and an increase trend for *P. vivax*.

Key words: malaria, children, mortality, South America, *Plasmodium vivax*.

Introduction

Morbidity and mortality burden of malaria in the childhood represents a public health threat not only in countries with high levels of transmission, but also in those, such as Venezuela and others in Latin America, with moderate to low levels of transmission. In general, malaria mortality in human populations varies largely under different circumstances. The intense malaria transmission conditions found in many parts of tropical Africa, the much lower malaria inoculation rates currently sustained in areas of Southeast Asia and the epidemic outbreaks of malaria occasionally seen in both the continents, present highly contrasting patterns of malaria-related mortality [1]. In the third malaria region, tropical Latin America, the epidemiological pattern is similar to Southeast Asia, where lower malaria inoculation rates are sustained with a significant difference in the prevalence of *Plasmodium vivax* infection, higher than *Plasmodium falciparum* ($\sim\geq$80% vs. $\leq$20%). Then in Asia and Latin America, lower malaria-related mortality are expected and seen.

Although malaria mortality, even in areas with predominant prevalence of *P. vivax* infections, has been mainly attributed to *P. falciparum*, few well-documented estimates of its direct and indirect burden exist [2]. Additionally, the changing patterns of increase in *P. vivax* malaria morbidity and mortality, particularly in children, are now causing concern.

In recent years, complicated and even fatal cases of malaria due to *P. vivax* have been increasingly reported in the medical literature, either in adults [3–9] and children [3, 10–18], particularly in countries with areas of high prevalence for this species, as occurs in Venezuela, but also as imported cases in distant countries [19–22]. In spite of this, no studies about *P. vivax* mortality in children compared to *P. falciparum* have been reported in Latin America. Our objective was to analyze the number of deaths directly attributable to malaria caused not just due to *P. falciparum* but also due to *P. vivax* in children in Venezuela for the years 1995 to 2004.

Methods

Epidemiological data for this study were retrieved from the records of the Ministry of Health in Venezuela. With these data, an analysis of malaria mortality burden in Venezuela during the study period was performed. Morbidity data were also analyzed for the studied period at the national level

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to perform further analyses beyond the primary analysis, and the objective of this report was to evaluate the trends in malaria mortality in Venezuela between 1995 and 2004. Malaria infection was confirmed in all cases with thick and thin blood smears, with external quality control. The different *Plasmodium* species were identified morphologically by laboratory experts dedicated to interpret malaria smears at the diagnostic units, and then confirmed at the Malariology Regional Offices in the endemic areas of Venezuela. In addition, all positive smears and 10% of those considered negative by the regional laboratories were reevaluated by a third national malaria reference microscopist to confirm the diagnosis of malaria and the etiological species.

We reviewed all mortality records from the Ministry of Health in Venezuela, using ICD-9 (084) and ICD-10 (B50-B54) codes to search for all deaths due to malaria during the study period. Mortality records were obtained from the compilation of the regional records in the whole country (24 states). Each of these integrated information of the municipalities' health offices (the basic level of administrative health reporting). Each death due to malaria was classified in the record according to the age and gender of the individual.

In Venezuela, malaria is officially reportable, with a weekly registry and reporting of morbidity. Additionally, all cases of deaths are specifically and obligatorily reportable, and mortality information is available and accurate. According to the World Health Organization (WHO) [23], the levels of evidence for all cause mortality and cause-specific mortality for Venezuela correspond to the level 2b (death registration data available for an earlier time period; completeness for latest year estimated using standard demographic methods for child deaths under age 5 and for deaths at ages 5 and over; estimated completeness used to adjust death registration data and then all cause mortality was calculated to the current year of mortality report).

Data were statistically processed to assess the importance, features and trends of fatal cases of malaria in Venezuela, particularly in children. Chi-squared and *F*-tests were used for comparison of qualitative and quantitative variables, respectively, and *p*-values less than 0.05 were regarded as significant. SPSS v.10.0®, Epi Info v.6.0 (CDC, Atlanta, GA, USA) and GraphPad Prism v.4 ® were used in the statistical analyses.

Results

For this period, 276 928 cases of malaria were registered in Venezuela (mean $27\,692.8 \pm 7593.0$ cases/year), with a significant increase from 1995 (22 056 cases) to 2004 (46 244 cases), more than 100% ($r^2 = 0.5501$, $F = 9.78$, $p = 0.014$) (Fig. 1A). By the end of this period, 38% of cases occurred in <20-year-old patients (20.9% in 10–19 year olds and 17.1% in <10-year-old children). The Annual Parasitic Index (API) (malaria cases/1000 population) for the period was 1.26 (ranging from 1.01 to 1.79). The burden of disease associated with malaria infection was mainly focused in the southern and northeastern regions of the country (Fig. 1B), where more than 90% of the cases occurred (just in three states, Bolivar, Amazonas and Sucre; first two are border states with Brazil) (Fig. 1B). The etiology was mainly due to *P. vivax* (85.5%, 2004).

From the total cases for the studied period, 407 patients died from malaria in Venezuela [case fatality rate (CFR) of 1.47‰ period range from 0.8 to 3.1], 66.34% (270) corresponded to deaths due to *P. falciparum*, 7.37% (30) to *P. vivax* and 0.74% to *Plasmodium malariae* (3) ($p < 0.01$) (in the rest, the species of *Plasmodium* were not recorded). From these deaths, as occurred with cases, more than 85% were recorded in just four states, three at the southern endemic area (Bolivar, Amazonas and Delta Amacuro) and one at the northeastern endemic area (Sucre) (Fig. 1B). Bolivar is the largest state of the country with area 238 000 km^2 and a population of 1 488 571 (2004). Along the period, 52.6% of malaria deaths of Venezuela occurred in this state with a mortality rate of 14.38 deaths/100 000 population; whilst in Amazon, the second largest state, 177 000 km^2, 105 497 population, that proportion was 26.8%, but this state presented the higher mortality rate, with 103.3 deaths/100 000 population.

The malaria mortality rate for the period was 0.19 deaths/100 000 population (ranging from 0.10 to 0.36) (Fig. 2A). The mean number of annual deaths was 40.7 ± 16.8 per year, showing a decreasing trend during the study period, but not significant ($r^2 = 0.3756$, $F = 4.82$, $p = 0.0595$) (Fig. 2A). Although the API slightly increased during the period, but not significantly ($r^2 = 0.1669$, $F = 1.603$, $p = 0.241$), the CFR decreased significantly through the period from 1995 (2.10‰) to 2004 (1.26‰) ($r^2 = 0.5701$, $F = 10.61$, $p = 0.0116$) (Fig. 2B).

The gender distribution was 62.9% males and 37.1% females ($p < 0.01$), with no significant variation during the study period and non-significant differences for the malaria due to *P. falciparum* or due to *P. vivax* ($p > 0.05$). The age distribution showed that deaths occurred in 28.3% in the age group of <10 years, followed by 15.7% in the group 20–29 years and 12.8% in the group 40–49 years ($\chi^2 = 140.19$, $p < 0.01$) (Fig. 3A). A total of 39.1% of registered deaths occurred in patients <20 years. In terms of age-adjusted mortality rate, among those in that age group, this was 1.6 deaths/100 000 boys <20 years. Differences were observed for these figures between *P. falciparum* and *P. vivax*. In *P. falciparum*, 29.3% of the deaths occurred in the age group of <10 years, whilst in *P. vivax*, this age

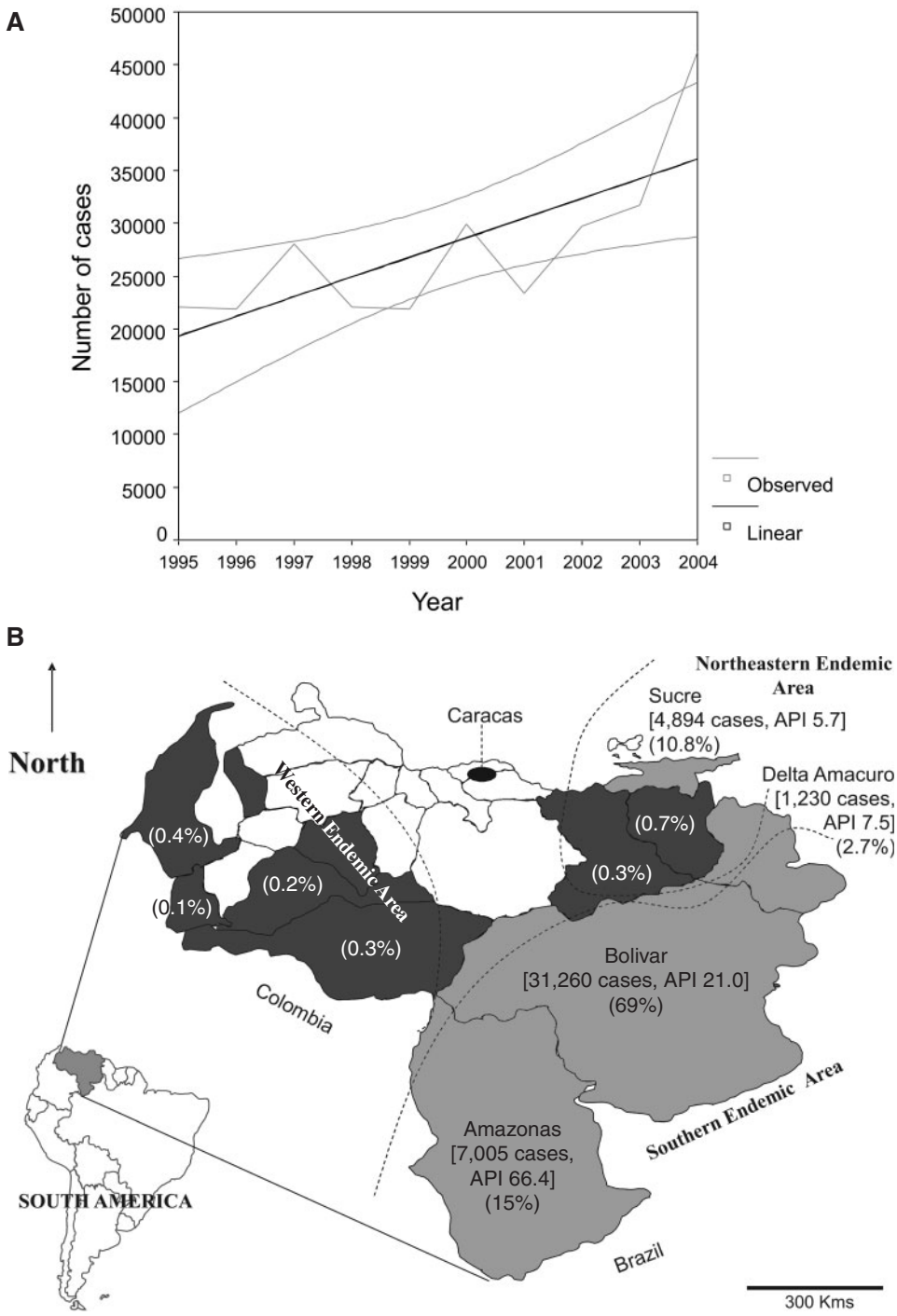

FIG. 1. Malaria incidence in Venezuela, 1995–2004 (**A**) and spatial distribution of cases for year 2004 (**B**) [28]. States in grey are those with high levels of transmission, contributing to more than 10% of country cases and/or an API (malaria cases/1,000 pop.) higher than 5.0; states in black are those with low-to-moderated levels of transmission, contributing to 0.1–10% of country cases and/or an API of 0.5–5.0, and states in white are those that are non-endemic.

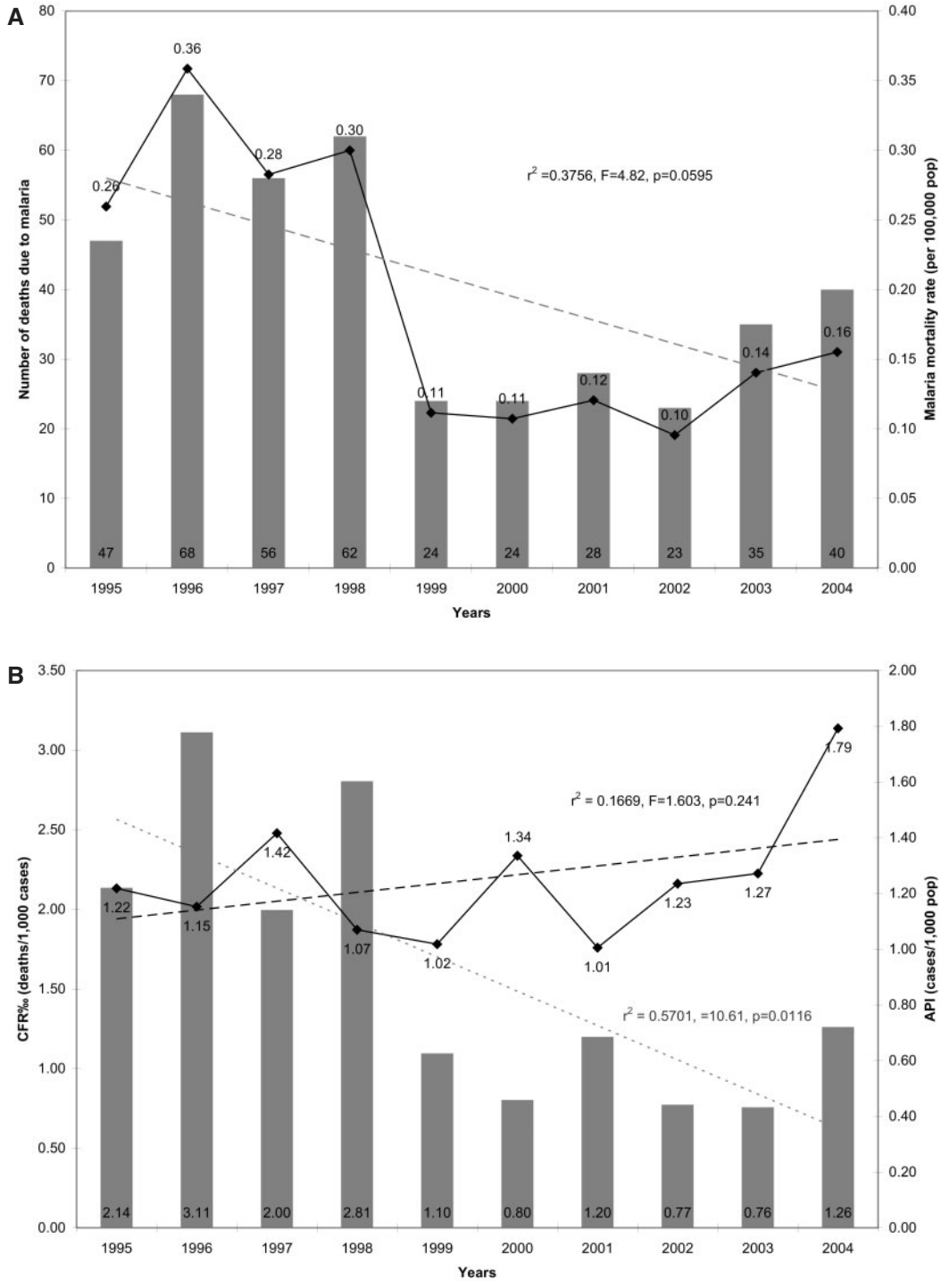

FIG. 2. Malaria mortality trend in Venezuela, 1995–2004. (**A**) Number of deaths due to malaria and malaria mortality rates; (**B**) CFR in malaria (‰) and API trends.

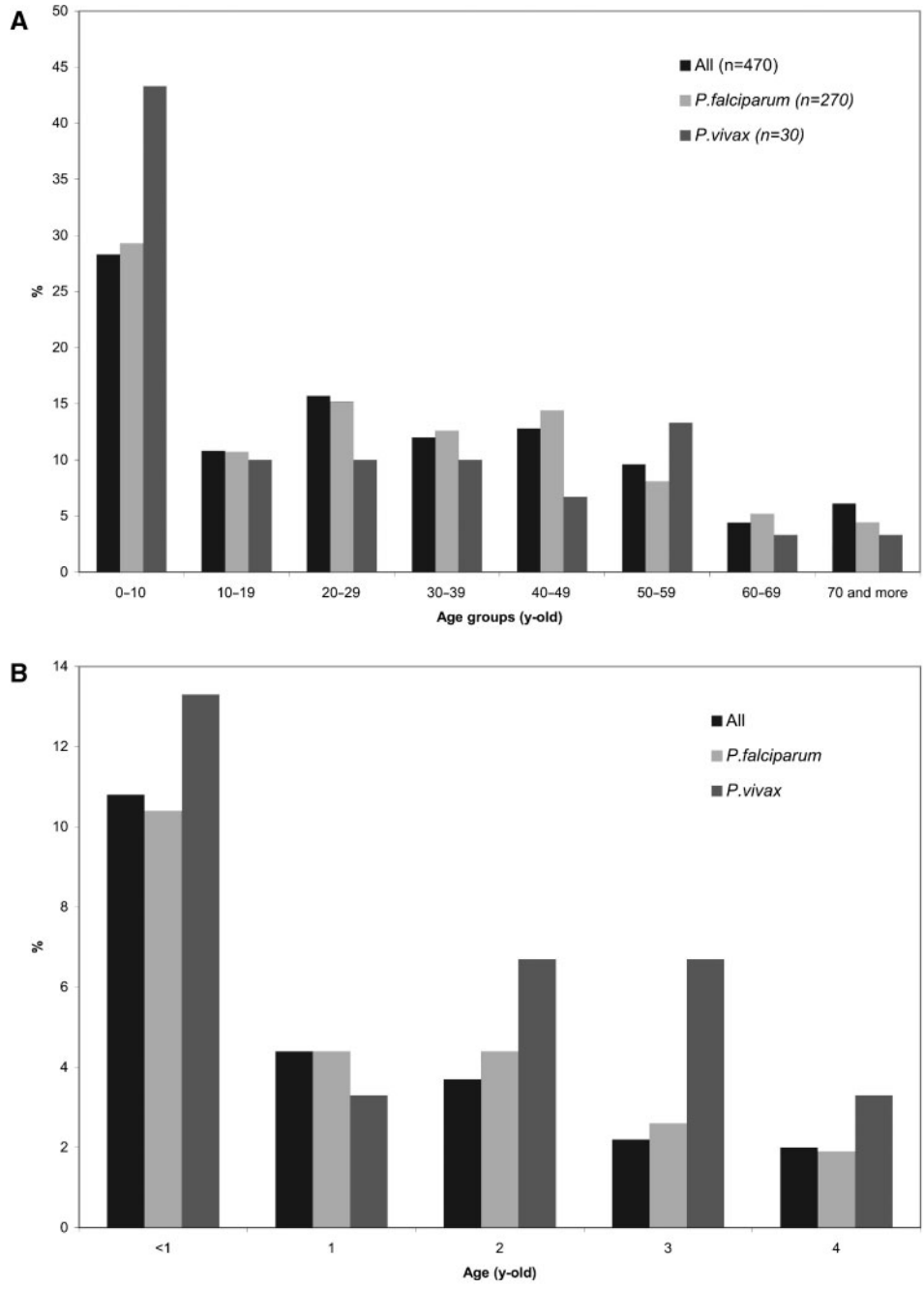

FIG. 3. Age distribution in deaths due to malaria in Venezuela, 1995–2004. (**A**) All age groups; (**B**) in those <5 years of age.

group represented 43.3% of the deaths due this species ($p = 0.113$) (Fig. 3A).

Deaths in young children (<5 years) represented 23.1% of total fatalities due to malaria, with an age-adjusted mortality rate of 3.8 deaths/100 000 children <5 years, being higher in those younger (Fig. 3B), with differences for these figures between *P. falciparum* and *P. vivax*. In *P. falciparum*, deaths

occurred in 10.4% in the age group of <1 year, whilst in *P. vivax*, this age group represented 13.3% of the deaths due this species ($p > 0.05$) (Fig. 3B). In the study period, only three deaths were registered as congenital cases of *falciparum* malaria (one death in 1997, 1998 and 2001, respectively). Additionally, the number of deaths as well the age distribution also varied, but significantly, among those patients <20 years who died from malaria along the period. During the years 1995, 1996, 1999, 2001 and 2002, deaths occurred in higher proportion in patients <1 year, compared with other periods ($p < 0.01$), differences in other age groups were also significant during the period ($p < 0.01$) (Fig. 4A). When we compared the states with higher number of cases and higher malaria mortality rates, we observed significant differences in the age distribution of deaths in <15 year olds. In Amazonas, 50.5% of deaths occurred in this age group (22.7% in <1 year olds), whilst in Bolivar that figure was just 22.2% (3.3% in <1 year olds, $p < 0.01$). The age-adjusted mortality rate also showed significant differences between these endemic states (Fig. 1B), being significantly higher in Amazonas (229.4 deaths/100 000 children <5 years) compared with Bolivar (12.5 deaths/100 000 children <5 years) ($p < 0.01$) (Fig. 4B). This difference pattern did not vary significantly along the period in these states.

From the total deaths due to *P. falciparum* (270), 25.93% (70) were classified as *P. falciparum* infection with brain malaria and 16.67% (45) as severe *falciparum* malaria. From the total deaths with brain malaria, 41.4% occurred in <20-year-old patients, 14.3% in those 10–19 years old and 27.1% in those <10 years (11.4% in <1 year). In those deaths due to *P. vivax* (30), 40% (12) were classified as due to *vivax* malaria with organic complications (e.g. splenic rupture); more than half of these deaths (7) occurred in children <10 years. The CFR was consistently higher in *P. falciparum* (range 3.78–15.61‰) along the period compared to *P. vivax* (range 0.00–0.31‰) ($p < 0.01$).

Finally, although in the studied period, just 30 deaths due to *P. vivax* were registered, with mentioned CFRs, compared to 270 due to *P. falciparum* with higher CFRs, the trends of both showed an inverse pattern, number of deaths due to *P. falciparum* is decreasing ($p = 0.0853$) and the number of deaths due to *P. vivax* is increasing ($p = 0.4866$) (Fig. 4C).

Discussion

According to the WHO at the end of 2004, 107 countries and territories had areas at risk of malaria transmission, for Latin America in nine countries that share the Amazon rainforest (including Venezuela) and in eight countries in Central America and the Caribbean [24]. Globally, an estimated 350–500 million clinical malaria episodes occur annually; most of these are caused by infection with *P. falciparum* and *P. vivax* [24]. Of these two species, *P. falciparum* is justifiably regarded as the greater menace because of the high levels of mortality with which it is associated (more than one million deaths each year), its widespread resistance to antimalarial drugs and its dominance on the world's most malarious continent, Africa. However, malaria due to *P. vivax* has also placed huge burdens on the health, longevity and general prosperity of large sections of the human population. The debilitating impact of *P. vivax* malaria remains high, unacceptable and in most situations, ultimately preventable for well over one billion inhabitants of the planet [25]. As introduced, complicated cases and even fatal cases of malaria due to *P. vivax* have been increasingly reported in the medical literature in the last 30 years, particularly in children [3, 10–18].

In 1974, Walzer *et al*. [26] reported two fatal cases of *P. vivax*, a Vietnam veteran with *P. vivax* infection who died with a ruptured spleen and a man with a previous splenectomy who died of a severe *P. vivax* infection acquired through blood transfusion. In the recent series of Kochar *et al*. (2005) [3] reporting on severe *vivax* malaria in 11 patients, 3 of them died; one of these a baby who died on the 14th day of life. Clinical data from these patients strongly indicate that *P. vivax* can cause both sequestration-related and non-sequestration-related complications of severe malaria [3–18], including cerebral malaria [3, 10, 11, 13], renal failure [18], circulatory collapse, severe anemia [7, 14], hemoglobinurea, abnormal bleeding, ARDS [8, 9, 16] and jaundice, all of which are commonly associated with *P. falciparum* infections [3]. These cases were confirmed with PCR without evidence of *P. falciparum* infections. In our study, although this additional molecular confirmation was not possible, it is important to mention that all positive smears for malaria and 10% of those considered negative by the regional laboratories were reevaluated by a third national malaria reference microscopist to confirm the diagnosis of malaria and the etiological species.

In this study, the burden of mortality due to malaria, although decreasing, is still significant, even in the setting of a significant increase of morbidity, which could be related with an early consultation, diagnosis and treatment of cases. More than a third of such morbidity occurs in the childhood and is focused in the southern region of the country. The mortality due to *P. falciparum* showed a similar pattern described in other countries with low to moderate levels of transmission and a high prevalence of *P. vivax* infections, but although herein only 30 deaths due to *P. vivax* are reported, the trends showed that the number of deaths due to *P. falciparum* is decreasing and the number of deaths due to *P. vivax* is increasing, with a significant proportion occurring

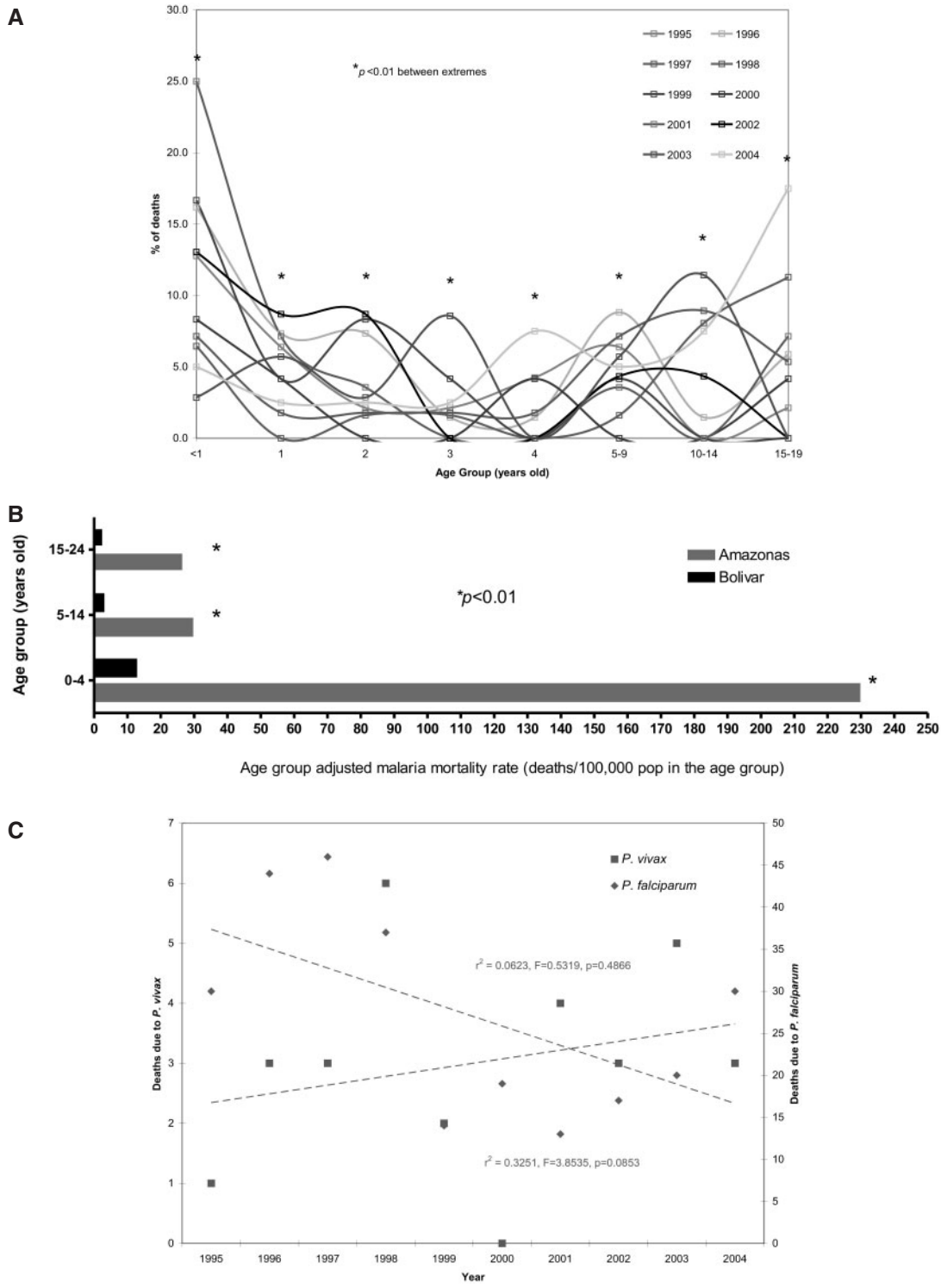

FIG. 4. Mortality trends in <20-year-olds with malaria (**A**), age-adjusted in Amazonas and Bolivar (**B**), and differences in etiology in Venezuela, 1995–2004 (species-related and linear trends) (**C**).

in children. Powerful antimalarial campaigns directed mainly to *P. falciparum* achieved a significant reduction of mortality, specially when compared to other periods, in terms of rates; 300.0 deaths/100 000 population before 1936, 112.0 between 1936 and 1944, from 62.5 in 1945 to 8.5 in 1950, <2.0 between 1951 and 1969, <1.0 between 1970 and 1994 and for the current period <0.5.

Historical evidence does indeed suggest that *P. vivax* imposed a significant burden of mortality that may have resulted from its interaction with other diseases and conditions. In the early 19th century in northern Europe, where malaria was entirely *vivax* or *quartan* malaria, the mortality rates doubled in the malarious areas; living in such areas costing the inhabitants a reduction of life expectancy at birth of ~20 years, compared to life expectancies at birth of 40–50 years in those who lived outside the malarious areas of England [25, 27]. In Sri Lanka, the malaria eradication efforts led to a major decrease in death rates in direct proportion to the previously high spleen rates recorded in endemic populations [25]. A significant proportion of the malaria burden in Sri Lanka then was due to *P. vivax* malaria, suggesting that *P. vivax* contributed significantly to mortality.

Although more detailed and prospective studies are required to measure the real impact of *P. vivax* mortality in children, particularly compared to *P. falciparum*, this study calls on the attention of severe disease and deaths due to a species which is likely to continually increase as a residual burden of malaria around the world, particularly in Southeast Asia and Latin America.

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