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Tuberculosis and malaria walk side by side in the Brazilian Amazon: an ecological approach

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Abstract

OBJECTIVE To assess the spatial distribution of TB and malaria incidence, as well as their spatial association with each other, regardless of environmental and socio-economic factors commonly reported as determinants of both disease rates among the municipalities of Amazonas State, Brazil between 2012 and 2015.

METHODS Through an ecological approach considering municipalities of Amazonas, Brazil, as unit of analysis, a negative binomial regression model was used to assess association between malaria and TB rates, in which the dependent variable was the average municipal tuberculosis incidence rate.

RESULTS Positive associations of overall malaria (β = 0.100 [CI = 0.032, 0.168], P = 0.004), *P. vivax* malaria (β = 0.115 [CI = 0.036, 0.195], P = 0.005), and *P. falciparum* malaria (β = 0.389 [CI = −0.0124, 0.791], P = 0.057) with TB rates were found, regardless of the sociodemographic factors included in the study.

CONCLUSION In the Brazilian Amazon, TB and malaria are spatially associated. Therefore, it is very likely that co-infections also occur in this region, regardless of the HIV status.

keywords tuberculosis, malaria, co-infection

Introduction

Tuberculosis (TB) is the world's leading killer among infectious diseases. Worldwide, more than 10 million people suffered from TB in 2017, of whom approximately 1.6 million died, including 300 000 people with HIV [1]. In the same year, in Brazil, 69 569 new cases and 13 347 TB recurrences were recorded, with an incidence rate of 33.5 per 100 000 inhabitants [2]. The incidence ranged from 20 per 100 000 inhabitants in midwestern to 43 in northern Brazil. In Amazonas State, where the highest rates have been reported, incidence was 74.1 per 100 000 inhabitants, and the mortality rate was the highest among states: 3.2 per 100 000 inhabitants, with the capital, Manaus, registering the highest rate in Amazonas (93.2 per 100 000 inhabitants) [2].

Malaria is also an infectious disease of high relevance to public health among tropical countries in Africa, Asia and Latin America. About 216 million malaria episodes occurred worldwide, and approximately 445 000 people died of malaria, which characterises it as a serious public health threat. In Brazil, where 450 000 cases were reported in 2017, malaria transmission occurs predominantly in the Amazon region (99.8% of cases) and is mainly caused by *Plasmodium vivax* and *Plasmodium falciparum* [3].

TB is associated with poverty, social exclusion and marginalisation, such as poor living conditions, and insufficient access to services and public goods [4]. The human epidemiological chain of malaria transmission includes human reservoirs, susceptible individuals and vectors [5,6]. Although these diseases being reported typically in different environments (urban and rural for TB and malaria, respectively), this territorial segregation is not completely valid for the Amazon region, since malaria transmission occurs in urban areas, and

populations from cities become infected in peripheral rural areas [5,7]. The Brazilian Amazon has several environmental, social and economic features that favour transmission of both diseases [8,9]. However, the available data on malaria–TB co-infection remain scarce.

Malaria is recognised for its immunomodulatory effects on the human host [10,11]. Malaria infection causes increased IFN-γ levels leading to a Th1-type pro-inflammatory response, with macrophage activation being essential in parasite clearance [12]. Macrophage, which plays a central role in the internalisation and intracellular control of *Mtb*, is also the primary phagocyte for the clearance of erythrocytes parasitised by *Plasmodium* sp. Interaction between malaria and tuberculosis *in vitro* and *in vivo* studies show that circulating monocytes, tissue macrophages and dendritic cells accumulating haemozoin present functional impairment by phagocytosing parasitised erythrocytes, losing their ability to control *Mtb* replication and NO production, resulting in the deregulation of the granulomas and consequently the activation of tuberculosis through the increase in the *Mtb* load [13].

This study assessed the spatial distribution of TB and malaria incidence, as well as their spatial association, in municipalities of Amazonas State, Brazil, from 2012 to 2015.

Methods

An ecological study was carried out based on epidemiological information surveillance of TB and malaria, in which the units of analysis were the municipalities of the state of Amazonas, Brazil. Anonymised secondary data from routine epidemiological surveillance database were used. The study was approved by the Research Ethics Committee of the Tropical Medicine Foundation of Amazonas.

The State of Amazonas is located in the Brazilian Western Amazon, comprising an area of 1 570 946.8 km^2,

Table 1 Number of cases of TB, *Plasmodium vivax* malaria, *Plasmodium falciparum* malaria and overall malaria by year and in the period of study

	2012	2013	2014	2015	Total
Tuberculosis	1407	1495	1453	1955	6310
P. vivax malaria	82 874	76 711	66 102	79 401	305 088
P. falciparum malaria	7186	9020	8291	6411	30 908
Overall malaria	90 060	85 731	74 393	85 812	335 996

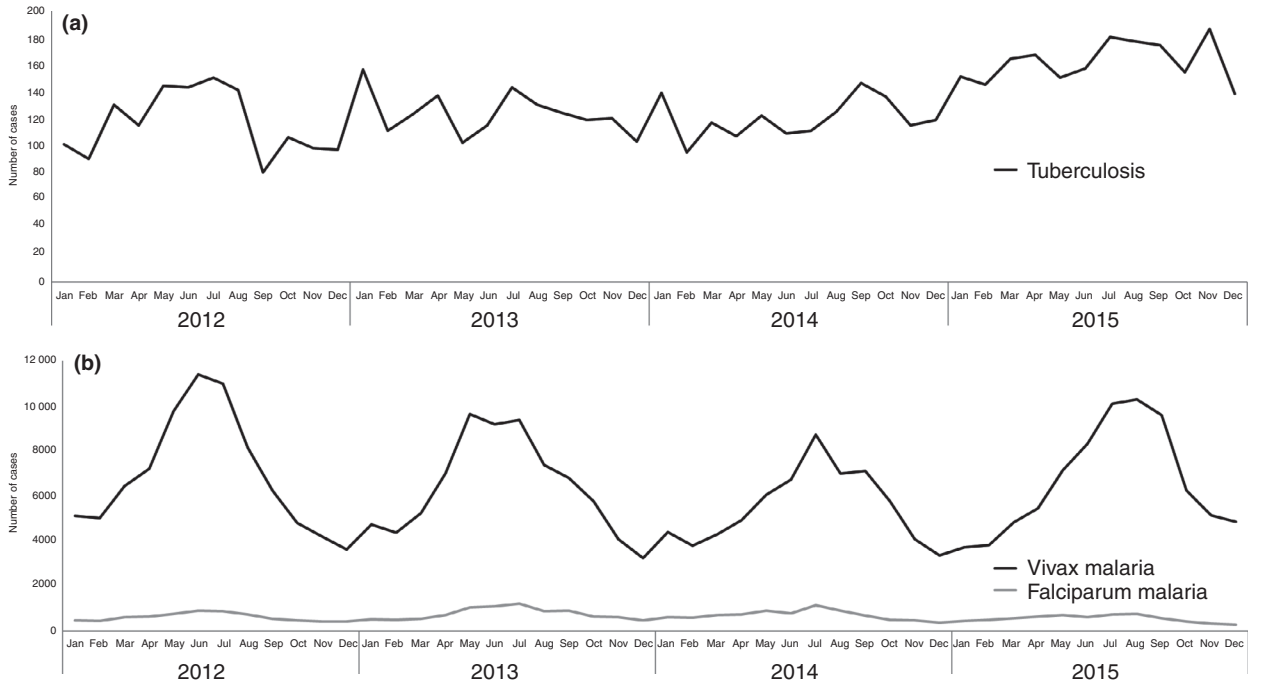

Figure 1 Monthly temporal distribution of malaria cases (*Plasmodium vivax* and *Plasmodium falciparum*) from 2012 a 2015 in Amazonas State (a). Monthly temporal distribution of pulmonary TB cases from 2012 a 2015 in Amazonas State (b).

with 62 municipalities divided politically into eight distinct administrative regions. The estimated population of the state was 3 807 921 inhabitants in 2010, with 74.2% of residents living in urban areas and 25.8% in rural areas [14].

All new cases of pulmonary TB with laboratory confirmation by sputum smear microscopy, rapid molecular test or culture in Amazonas State officially reported to the National Information System of Reportable Diseases (SINAN) were included in the study. Likewise, all the positive cases of malaria caused by *P. vivax* and *P. falciparum*, with laboratory confirmation by thick blood smear reported to National Epidemiological Surveillance Information System for Malaria Report (SIVEP Malaria) were included from January 2012 to December 2015. TB recurrences and HIV co-infections were excluded.

Socio-economic data used were as follows: Municipal Human Development Index (MHDI), Gini index for income (income inequality of heads of households), percentage of people with per capita income below half the minimum wage, unemployment rate of the population aged 18 or over; and population density. For these variables, data from 2010, collected by the United Nations Development Program (UNDP – http://www.br.undp.org/) were used. In addition, a variable that measures the performance of health services, called the Health System Performance Index (IDSUS – http://idsus.saude.gov.br/), was included in the model. This variable is composed of indicators of access and effectiveness for 2010.

To study the association between malaria and TB incidence rates within municipalities, considering the socioeconomic and health system performance variables mentioned above, a negative binomial regression model was used. Collinearity and interaction between the explanatory variables were evaluated in the analysis that led to the final model. The dependent variable was the average municipal tuberculosis incidence rate. For malaria incidence rates, different numerators were considered in order to have independent variables representing both different parasitic species (*P. vivax* and *P. falciparum*) and the burden of malaria (overall malaria cases). Socioeconomic and health system performance variables were used as covariables in the model. A stepwise regression

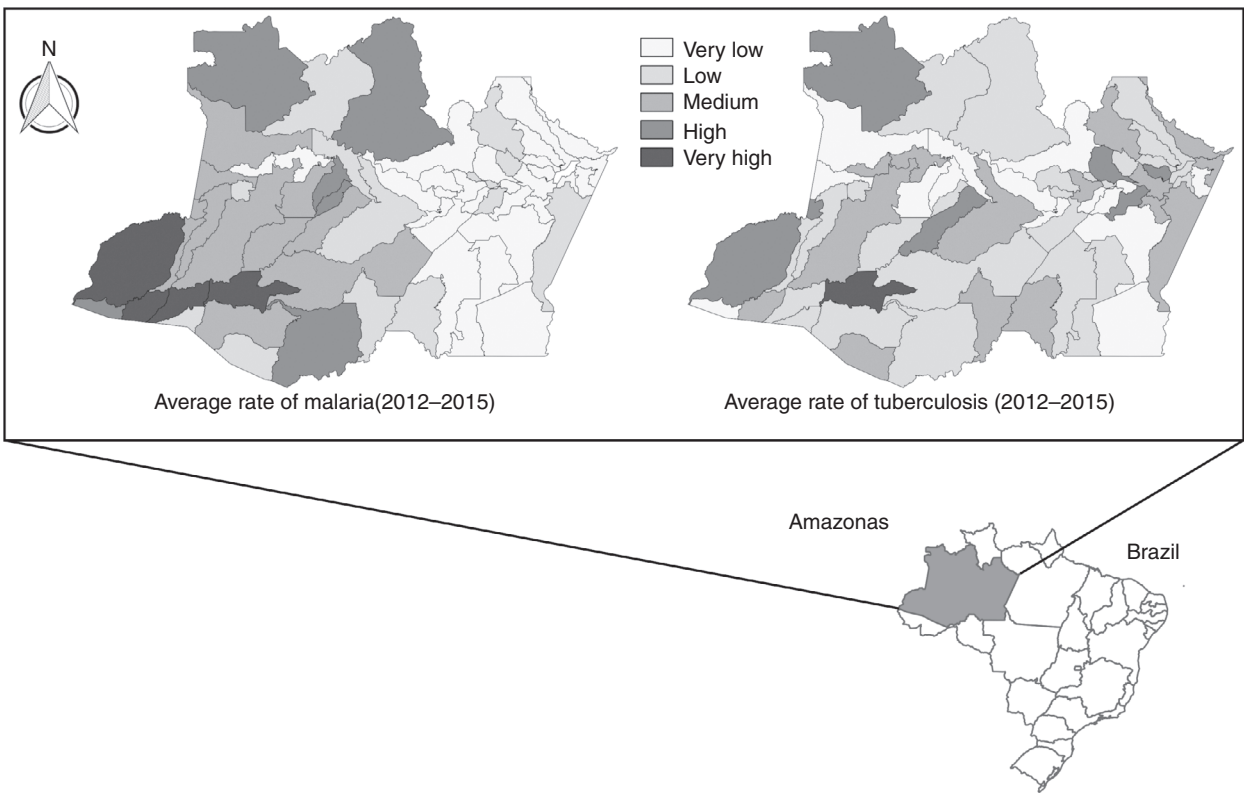

Figure 2 Spatial distribution of TB and malaria average rates within Amazonas municipalities throughout the years of the study.

Table 2 Overall malaria and other factors associated with pulmonary TB average rates of Amazonas municipalities 2012 to 2015

Average tuberculosis rate	Mean ± SD	Min.	Max.	Crude β (CI 95%)	*P*-value	Adj. β (CI 95%)	*P*-value
Average malaria rate	47.68 ± 67.60	0.137	291.11	0.070 (0.006, 0.134)	0.032	0.100 (0.032, 0.168)	0.004
Unemployment rate of the population aged 18 and over	7.64 ± 3.28	1.6	18.92	0.00073 (−1.374, 1.375)	0.999	–	–
Percentage of people living with inadequate sanitation	37.6 ± 14.92	6.45	72.6	−0.209 (−0.506, 0.087)	0.164	0.065 (−0.252, 0.385	0.680
Percentage of urban population	44 443.39 ± 226 152.5	1000	1 792 881	0.0000251 (6.23e-06, 0.0000439)	0.010	5.11e-07 (−0.001, 0.001)	0.993
Index of municipal human development	565.112 ± 53.84	450	737	0.057 (−0.025, 0.139)	0.171	0.130 (0.032, 0.228)	0.010
Percentage of poor people	53.02 ± 11.98	12.9	74.2	−0.232 (−0.603, 0.139)	0.216	−0.318 (−0.978, 0.341)	0.338
Gini index for income	61.98 ± 5.86	52	80	0.86 (0.134, 1.604)	0.021	0.925 (0.206, 1.644)	0.013
Index of health system performance	23.38 ± 6.15	10.18	37.66	0.45 (−0.270, 1.175)	0.216	0.191 (−0.609, 0.991)	0.634
Demographic density	5.80 ± 21.17	0.11	166.54	0.2580 (0.055, 0.460)	0.013	0.156 (−0.052, 0.366)	0.139

with backward selection was carried out. Variables with a *P*-value ≤ 0.2 were kept in the model. The final model was defined once all remaining variables had a *P*-value of ≤ 0.05.

Statistical analyses were performed using the statistical package STATA v.13 (USA) and maps created with QGIS software 2.12.3 (USA).

Results

Distribution of diseases

Table 1 describes the number of malaria and TB cases from 2012 to 2015. Notably, malaria case records peaked in June and July with high transmission season from April to September and low transmission from October to March of the next year (Figure 1b). Conversely, the number of TB cases progressively increased over the years, presenting a balanced distribution with peaks in the months of June, July, December and January (Figure 1a). Comparing temporal distribution profile of both diseases, a similar seasonal pattern is observed (Figure 1).

The spatial distribution of incidences of both diseases points to a concentration of high incidence in the Rio Negro and Solimões regions; municipality of Manaus; and Juruá. When comparing the distributions of the rates of both diseases, the municipalities of Itamarati (Juruá), São Gabriel da Cachoeira (Alto Rio Negro) and Jutaí (Alto Solimões) presented the highest rates. In contrast, the municipalities of Rio Madeira and Rio Negro e Solimões regions presented the lowest rates (Figure 2).

In univariable analysis, the average malaria rate (β = 0.070 [CI = 0.006, 0.134], *P* = 0.032), the percentage of urban population (β = 0.0000251 [CI = 6.23e-06, 0.0000439], *P* = 0.010), Gini index for income = 0.86 [CI = 0.134, 1.604], *P* = 0.021) and population density (β = 0.2580 [CI = 0.55, 0.460], *P* = 0.013) were positively associated with the average incidence rate of TB in municipalities (Table 2). In the same analysis, there was no association between the dependent variable and the unemployment rate of the population aged 18 years or older (β = 0.00073 [CI = 1.374, 1.375], *P* = 0.999), percentage of people living with inadequate sanitation (β = 0.057 [CI = −0.603, 0.139], *P* = 0.171), percentage of poor people (β = −0.232 [CI = −0.603, 0.139], *P* = 0.216) and the performance index of the health system (β = 0.45 [CI = −0.270, 1.175], *P* = 0.216) (Table 2).

When the overall average malaria rate per municipality was considered as an independent variable, the final model revealed a positive association with TB rates

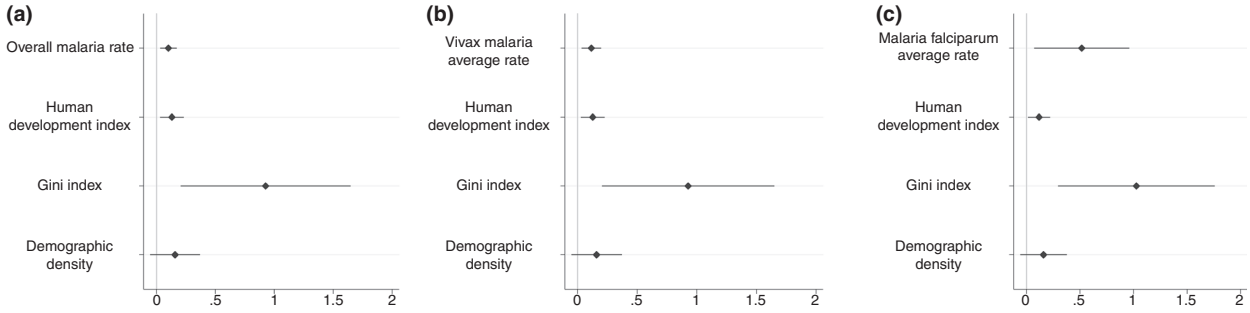

Figure 3 Forest plot of regression coefficients of municipal human development index, Gini index for income, demographic density and (a) average overall malaria rates (b) *Plasmodium vivax* malaria average rate and (c) *Plasmodium falciparum* malaria average rate.

(β = 0.100 [CI = 0.032, 0.168], P = 0.004), regardless of the sociodemographic factors included in the study as follows: municipal human development index (β = 0.130 [CI = 0.032, 0.228], P = 0.010), and Gini Index (β = 0.925 [CI = 0.206, 1.644], P = 0.013) (Figure 3). Although there was no statistical significance in the association between the dependent variable and population density (β = 0.156 [CI = −0.052, 0.366], P = 0.139), this variable was kept in the final model because of its importance as a social determinant. Percentage of people living with inadequate sanitation (β = −0.065 [CI = −0.252, 0.385], P = 0.680), percentage of urban population (β = 5.11e-07 [CI = −0.001, 0.001], P = 0.993), percentage of poor people (β = −0.318 [CI = −0.978, 0.341], P = 0.338) and the performance index of the health system (β = 0.191 [CI = −0.609, 0.991], P = 0.634) were not associated in the multivariate approach (Table 2).

When *P. vivax* malaria rate was considered as an explanatory variable, a positive association (β = 0.115 [CI = 0.036, 0.195], P = 0.005) was observed with the outcome, independently of the sociodemographic factors of the previous model: municipal human development index = 0.057 [CI = −0.025, 0.139], Gini index for income (β = 0.927 [CI = 0.206, 1.647], P = 0.013) and population density (β = 0.160 [CI = −0.493, 0.369], P = 0.131) (Table 3).

The analysis that considered average malaria rate by *P. falciparum* as an explanatory variable, showed a positive association with the outcome (β = 0.389 [CI = −0.0124, 0.791], P = 0.057), regardless of Gini index for income (β = 0.316 [CI = 0.498, 2.135], P = 0.002), population density (β = 0.148 [CI = −0.067, 0.365], P = 0.175) and percentage of poor people (β = −0.569 [CI = −1.032, −0.106], P = 0.017), which also showed association with pulmonary TB rates in municipalities (Table 4).

Discussion

We found an ecological association between pulmonary TB and malaria rates in Amazonas State, a region with high rates of both diseases. We also demonstrated association between the outcome and malaria rates for overall burden of disease and distinct parasite species.

The spatial distribution of pulmonary TB incidence showed a heterogeneous pattern over the years in the cities and regions of state of Amazonas with higher rates, in places with higher proportions of indigenous people, as also demonstrated elsewhere [9]. This finding reinforces the important role that strategies focusing TB control in special neglected populations plays in Amazon.

The transmission progression of both TB and malaria is strongly influenced by socio-economic factors, which why they were included in the present study [15–18]. The retrospective design based on data obtained from two different public health information systems is a limitation to the study, since the variables assessed are restricted to the data collected and the quality of the surveillance systems. However, the large number of reported cases in such a wide area tends to decrease bias in the reporting system. Limitations of the ecological approach include unmeasured confounders, which in this case would be predominantly social and economic factors. Although more sociodemographic variables have been assessed, collinearity analysis was decisive to not inflate the models with any dimension and still keep important aspects of sociodemographic measures.

Several studies have demonstrated modulations of the immune system during co-infections affecting host response and thus the pathophysiology of diseases. Some of these showed that the immune response was modified in the co-infection of TB and parasitic diseases, like

Table 3 *Plasmodium vivax* malaria and other factors associated with pulmonary TB average rates of Amazonas municipalities 2012 to 2015

Average tuberculosis rate	Mean ± SD	Min.	Max.	Crude β (CI 95%)	*P*-value	Adj. β (CI 95%)	*P*-value
Average malaria *vivax* rate	41.75 ± 57.6	0.138	218.50	0.082 (0.007, 0.157)	0.032	0.115 (0.036, 0.195)	0.005
Unemployment rate of the population aged 18 and over	7.64 ± 3.28	1.6	18.92	0.00073 (−1.374, 1.375)	0.999	–	–
Percentage of people living with inadequate sanitation	37.6 ± 14.92	6.45	72.6	−0.209 (−0.506, 0.087)	0.164	–	–
Percentage of urban population	44 443.39 ± 226 152.5	1000	1 792 881	0.0000251 (6.23e-06, 0.0000439)	0.010	–	–
Index of municipal human development	565.112 ± 53.84	450	737	0.057 (−0.025, 0.139)	0.171	0.127 (0.029, 0.224)	0.011
Percentage of poor	53.02 ± 11.98	12.9	74.2	−0.232 (−0.603, 0.139)	0.216	–	–
Gini index	61.98 ± 5.86	52	80	0.86 (0.134, 1.604)	0.021	0.927 (0.206, 1.647)	0.013
Index of performance of the Unified Health System	23.38 ± 6.15	10.18	37.66	0.45 (−0.270, 1.175)	0.216	–	–
Demographic density	5.80 ± 21.17	0.11	166.54	0.2580 (0.055, 0.460)	0.013	0.160 (−0.0493, 0 .369)	0.131

Table 4 *Plasmodium falciparum* malaria and other factors associated to pulmonary TB average rates of Amazonas municipalities 2012 to 2015

Average tuberculosis rate	Mean ± SD	Min.	Max.	Crude β (CI 95%)	*P*-value	Adjusted β (CI 95%)	*P*-value
Average P. *falciparum* malaria rate	5.25 ± 10.44	0	6.253.842	0.361 (−0.059, 0.783)	0.091	0.389 (−0.0124, 0 .791)	0.057
Unemployment rate of the population aged 18 and over	7.64 ± 3.28	1.6	18.92	0.00073 (−1.374, 1.375)	0.999	–	–
Percentage of people living with inadequate sanitation	37.6 ± 14.92	6.45	72.6	−0.209 (−0.506, 0.087)	0.164	–	–
Percentage of urban population	44 443.39 ± 226 152.5	1000	1 792 881	0.0000251 (6.23e-06, 0.0000439)	0.010	–	–
Index of municipal human development	565.112 ± 53.84	450	737	0.057 (−0.025, 0.139)	0.171	–	–
Percentage of poor	53.02 ± 11.98	12.9	74.2	−0.232 (−0.603, 0.139)	0.216	−0.569 (−1.032, −0.106)	0.017
Gini index	61.98 ± 5.86	52	80	0.86 (0.134, 1.604)	0.021	1.316 (0.498, 2.135)	0.002
Index of performance of the Unified Health System	23.38 ± 6.15	10.18	37.66	0.45 (−0.270, 1.175)	0.216	–	–
Demographic density	5.80 ± 21.17	0.11	166.54	0.2580 (0.055, 0.460)	0.013	0.148 (−0.067, 0.365)	0.175

malaria, presenting important evidences in murine models and cell culture [19,20]. In a murine model, individuals co-infected with latent tuberculosis were submitted to a non-lethal strain of *Plasmodium yoelii*. They showed an increase in TNFα levels and recrudescence of CD11c + cells from the lungs. These CD11c + cells are responsible to promote the survival and growth of Mtb, resulting in the increase in inflammatory mediators and the infiltration of cells in the lung, demonstrating the transient exacerbation of the disease [21].

To understand the biological interaction between these two pathogens *in vivo*, infected mice with Mtb and, eight weeks later, with a non-lethal *P. yoelii* strain, showed that the co-infected mice were less able to contain the growth of Mtb in the lung, spleen and liver, thus increasing mortality [22]. These results those of studies that demonstrate activation of TB after malaria exposure – evidence that malaria parasites can suppress host cellular and humoral immune responses during *Mycobacterium tuberculosis* (Mtb) infection [23]. Disease control strategies for populations for which both diseases are endemic should consider the influence of increased incidence of one infection on the other [22].

A study pointed to a significant association with the increase in the probability of living in a sector with higher case density. Previous studies have described that households clearly represent areas of intense Mtb transmission, strengthening the idea that regions with a higher density of people living in the same area are at higher risk of becoming infected and developing the disease [24,25]. The lack of development plans for these communities could be contributing to the population density increase which in turn, plays an important role in the transmission of both TB and malaria.

Income inequality, as measured by the income Gini index, was another social factor that showed association with the incidence of TB in the municipalities, corroborating the study by Castro et al., 2016, which observed similar results. Economic inequality seems to have great influence on diverse population conditions, influencing health status and transmission of tuberculosis and malaria [16,26].

The TB incidence among municipalities of state of Amazonas was also positively associated with the MHDI. It should be noted here that the data used refer to the notifications reported in official information systems of the Ministry of Health that are conditioned to the ability of the health system to detect infections, suggesting that such an association may imply better ability of detection of the disease by the system and not necessarily a causal relationship [27].

Conclusion

Malaria and TB have had a direct impact on human populations, especially in the tropics, impacting international health. Both infectious diseases are implicated in high mortality worldwide and a major problem in low-income and middle-income countries. In the Brazilian Amazon, TB and malaria are spatially associated. Association of both diseases at individual levels influencing transmission of these infections is to be further explored through cohort or case–control studies in order to assess both time to event and causal associations. It is very likely that co-infections also occur in this region, regardless of the HIV status. Further studies that assess how the interaction between these two infections can affect the incidence and prognosis of co-infected individuals are needed.

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