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1 **Interactions between gastro intestinal nematodes and malaria in a cohort of children in an**
2 **Amazonian village.**

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18 **Summary**

19 **Introduction.** Most studies on nematode malaria interactions were conducted outside of the Americas.
20 The objective of the present study was thus to study the relation between malaria and nematodes in a
21 cohort of children in an Amazonian village.

22 **Methods.** Odds ratios for intestinal nematode infections as an explanatory variable to malaria-resistant
23 vs. malaria-sensitive were computed.

24 **Results.** *Ascaris lumbricoides* was significantly more frequent in the “resistant” malaria group than in
25 the “sensitive” one.

26 **Conclusions.** Despite its low statistical power, the present results find that **Ascaris** was associated
27 with less malaria, as observed by a number of studies.

28

29 **Keywords:** *Plasmodium falciparum*, *Plasmodium vivax*, relapses, GI nematodes, *Ascaris*
30 *lumbricoides*, French Guiana.

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35 **Introduction**

36 Gastrointestinal nematode infections and malaria have a broadly overlapping distribution. A number
37 of studies from different continents have shown complex interactions between different GI nematodes
38 and malaria.

39 Observational studies in Thailand showed that *Ascaris lumbricoides* was associated with a dose-
40 dependent association with protection from cerebral malaria and acute renal failure ^{1, 2}. Other studies
41 have shown that *Ascaris* was associated with lower incidence or prevalence of malaria ^{3, 4}. In contrast,
42 it was observed notably in Africa and Madagascar, that hookworm was associated with a greater
43 incidence of malaria ⁵⁻⁹.

44 These research questions have received relatively little attention given the omnipresence of
45 coinfections in tropical regions. The difficulty of this question lies in the different dynamics of
46 transmission between malaria and different helminthes with different immunomodulatory properties or
47 hematologic consequences, which complicates the analysis of results. In addition, most results come
48 from observational studies which are prone to biases and confounding (nutritional status,
49 socioeconomic level, anemia, background immunity, self-treatment, etc.).

50 In French Guiana, studies performed in 2000 - 2005 (unpublished data) have shown the persistence of
51 a high prevalence of gastrointestinal nematode infections among communities living in the interior of
52 French Guiana, particularly among Amerindian children living along the middle and upper Oyapock
53 River (Camopi, Trois-Sauts). The most frequent parasite species were *Ascaris lumbricoides*,
54 *Strongyloides stercoralis*, and *Necator americanus*. These studies have shown a prevalence exceeding
55 20% for these three nematodes.

56 In parallel, the incidence of malaria was high among children (0-7 years) in Camopi over the 2001-
57 2009 period with a mean of 238, 514 and 21‰ person-years for *P. falciparum*, *P. vivax* and mixed
58 infections (microscopic diagnosis), respectively. Finally, a univariate Cox regression analysis showed
59 that there was a link between anthelmintic treatment and malaria in these children ¹⁰.

60 The trends suggest that while malaria seems less symptomatic among *Ascaris*-infected persons than
61 those without *Ascaris*, it seems that incidence is higher among patients with hookworm than those
62 without hookworm. This may result from immune modulation in *Ascaris*-infected patients and
63 hematologic factors in hookworm-infected patients. Although discernible trends seem to emerge, there
64 are conflicting results, which are often due to methodological differences. It is impossible to
65 demonstrate causal relations in observational studies. However, converging elements may point to
66 causal relations between two variables. To this end repeating the study in different contexts is
67 important to determine if a finding is robust. Most studies on GI-nematode malaria interactions were
68 conducted outside of the Americas except two studies in Colombia and Brazil ^{4,7}. The objective of the
69 present study was thus to determine whether there were any relation between malaria and GI
70 nematodes in the context of a cohort of children under seven years of age living in a small Amazonian
71 village in French Guiana.

72 **Methods**

73 The village of Camopi, located in the Oyapock malaria endemic area, consists of a central village and
74 28 hamlets localized within 15 km² along the Oyapock and the Camopi Rivers. The village is isolated
75 from the coast and separated from Brazil by the Oyapock River, which represents the border. The
76 1200 inhabitants of Camopi are mainly Wayampi and Teko Amerindians from the linguistic family of
77 the tupi-guarani. They respectively live on the banks of the Oyapock and the Camopi Rivers. The
78 population is young with an average age of 18 years.

79 The patients from the Camopi cohort described elsewhere^{10, 11} were reviewed and classified in two
80 groups, one resistant and one sensitive according to the number of malaria episodes. *Plasmodium*
81 *vivax* relapses were defined as infections occurring within 90 days of a first *P. vivax* episode ¹².

82 Two groups of children were identified regarding their past history of malaria infection in the period
83 2001-2009: one "sensitive" group had ≥ 7 malaria episodes; and one "resistant" group only had ≤ 1
84 within 3 years or ≤ 2 within 6 years.

85 Subsequently to this group definition, three field missions were conducted to collect stool samples in
86 order to test the hypothesis that malaria-resistant patients had a significantly different prevalence of GI
87 nematodes than the "malaria-sensitive" group.

88 Overall 91 stool samples were collected. All past malaria history, nematodes infection and
89 anthelmintic treatments were recorded for each child included in the study.

90 Laboratory diagnosis of three helminth infections was performed by multiplex real-time PCR (*Ascaris*
91 *lumbricoides*, *Necator americanus* or hookworm, and *Strongyloides stercoralis* or threadworm) ¹³.

92 Odds ratios for intestinal nematode infections as an explanatory variable to malaria-resistant vs.
93 malaria-sensitive were computed with Stata 10® software (College Station, Texas).

94 Odds ratios for intestinal nematode infections as an explanatory variable to « relapses » vs. « no
95 relapses» were also computed. Given the small number of observations multivariate analyses were
96 not used.

97

98 **Results**

99 Overall 86.8% of the children were infected by one nematode: 68.1% (n=62) were infected by
100 hookworm, 52.7% (n=48) by threadworm and 34.1% (n=31) by *Ascaris*. A total of 65% of the
101 children had a co-infection.

102 Coinfections between *N. americanus* and *S. stercoralis* were more frequent than coinfections with
103 *Ascaris*(see Figure 2). This is probably because hookworm and threadworm are present in the same
104 environmental types due to their similar modes of transmission.

105 Among the 91 children who participated in the study, 84 were included. A total of 41 children were
106 “malaria sensitive” and 43 of them were “malaria resistant” regarding the chosen group definition.

107 Table 1 shows that *Ascaris* was significantly more frequent in the “resistant” malaria group than in the
108 “sensitive” one (p=0.003). No association was found between the two other nematodes and malaria.

109 Among the 57 children that had at least one *P. vivax* episode, 41 had one or more relapses whereas 16
110 children had no relapses. *Ascaris* was more frequent in children that had no relapses but this failed to
111 reach statistical significance. Table 1 shows that relapses seemed less frequent in the *Ascaris* group.
112 The difference was not significant but the power to detect such a difference given the sample size was
113 only 30%.

114 **Discussion**

115 Despite its very low sample size, the present study, as a number of other studies^{1, 3, 4, 7, 14} reviewed¹⁵,
116 has found a negative association between *Ascaris* and malaria in this Amazonian setting. To explain
117 the proximal explanation of these observations between *Ascaris* and malaria, complementary
118 immunological hypotheses have been put forward{Nacher, 2002 #40}. This reinforces the suggestion
119 that *Ascaris* has a protective impact on both the severity and patency of clinical infections. *Ascaris*
120 *lumbricoides* has often been singled out as the most significant worm presumably because it also
121 represents the one with the largest biomass of antigenic immunomodulatory material. In addition,
122 *Ascaris* antigens have been reported to have a particular ability to induce a strong IgE response.
123 Hypothetical ultimate causes lie in the mutual benefits for the worm and malaria parasites to protect
124 their host in order to reproduce more effectively. Patients co-infected with malaria and a nematode
125 seem to have more gametocytes, fewer symptoms associated with malaria and infection of longer
126 duration. The anemic host has an increased attractiveness of the host for the vectors presumably
127 leading to an increase of the number of mosquito bites. This phenomenon could affect incidence and
128 transmission.

129 Although the results were not statistically significant at the 5% level, there was a trend for decreased
130 relapses in *Ascaris*-infected patients. Surely, statistical power was much too low (28%). The
131 hypothesis is again that *Ascaris*-mediated immunomodulation may interfere with the activation of
132 latent hypnozoites leading to the *vivax* relapses. This had never been shown before. Given the novelty
133 and implications of such an observation, larger studies should test this hypothesis.

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135 The weakness of the present study was its sample size. However, despite its low statistical power the
136 present results also find that *Ascaris* was associated with less malaria, as observed by a number of
137 studies. An interesting corollary finding was that there also seemed to be fewer *P.vivax* relapses in the
138 *Ascaris* group which would be a novel observation with intriguing implications on the activation of
139 latent hypnozoites. However, this observation needs to be replicated with larger sample sizes. This
140 data from South America brings additional data to further improve the understanding of nematodes-
141 *Plasmodium* coinfections.

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145 **Conflict of interest statement:** The authors declare that there is no conflict of interest.

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148 **References**

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