Mini Review

Could *Plasmodium vivax* malaria trigger malnutrition? Revisiting the Bradford Hill criteria to assess a causal relationship between two neglected problems

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Abstract

The benign characteristics formerly attributed to *Plasmodium vivax* infections have recently changed owing to the increasing number of reports of severe vivax malaria resulting in a broad spectrum of clinical complications, probably including undernutrition. Causal inference is a complex process, and arriving at a tentative inference of the causal or non-causal nature of an association is a subjective process limited by the existing evidence. Applying classical epidemiology principles, such as the Bradford Hill criteria, may help foster an understanding of causality and lead to appropriate interventions being proposed that may improve quality of life and decrease morbidity in neglected populations. Here, we examined these criteria in the context of the available data suggesting that vivax malaria may substantially contribute to childhood malnutrition. We found the data supported a role for *P. vivax* in the etiology of undernutrition in endemic areas. Thus, the application of modern causal inference tools, in future studies, may be useful in determining causation.

Keywords: *Plasmodium vivax*. Malaria. Malnutrition. Causation. Epidemiology.

INTRODUCTION

Global estimates for 2013 indicated that 161 million children less than 5 years of age demonstrated stunted development, 99 million were underweight, and 51 million showed evidence of wasting. Nearly half of all deaths in this population are attributable to undernutrition, translating into the unnecessary loss of about 3 million young lives each year[1]. Undernutrition increases the frequency and severity of both common and unusual infections, and leads to less effective anti-infective therapy. Therefore, undernutrition contributes to delayed recovery and increases the mortality risk of children with such conditions. Additionally, infection can contribute to the worsening of an individual's nutritional status, creating a potentially lethal cycle of worsening illness and deteriorating nutritional status[2].

Establishing causal associations in epidemiology is challenging due to the complexity, diversity, and multiplicity of involved components[3], especially as they relate to nutritional outcomes[4]. The development of novel and more sophisticated analytical procedures for causal inference has received considerable attention and has resulted in recent advances. In a scenario of increasingly complex primary health care actions and constrained financial and human resources, a better understanding of the factors associated with nutritional status is important for improving health care planning and improving the performance of public health systems[5]. Causal inference is a complex process that remains a major challenge in epidemiology. With the currently available knowledge, arriving at the tentative inference of a causal or non-causal nature of an association is an appealing scientific exercise, but generally a subjective process. Indeed, this process is more intricate when it involves multicausal phenomena, such as undernutrition, in which every causal mechanism involves the joint action of a multitude of components[3].

Classically, the causes of undernutrition can be divided into *immediate, underlying,* and *basic* causes[6]. Immediate causes include poor diets, with low-quality meals lacking nutrient density or variety, and infrequent or insufficient feeding. Chronic and acute diseases, particularly human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), diarrhea, respiratory tract or ear infections, measles, and hookworms and other gut parasites, represent other immediate causes of undernutrition. The causal pathway is usually further complicated by underlying socioeconomic factors, such as family food insecurity, inadequate care of vulnerable household members, inadequate sanitary living conditions (e.g., poor water supplies and poor sanitation), and inadequate health care services. Collectively, poverty, lack of information, political and economic insecurity, war, a general lack of resources, unequal status of women, and/or natural disasters act as the basic causes of undernutrition. The causal pie model suggests that these multiple components act complementarily (in either an additive or multiplicative association) to result in undernutrition[3].

To control undernutrition in certain areas, the essential task remains determining the most prevalent causes of the condition and establishing preventive and treatment measures at different levels. However, in general, several possible undernutrition causes overlap one another in developing regions of the world, and these affect the methodological capacity for controlling all potential confounders in epidemiological studies. This has been the main criticism of studies aiming to define the causes of undernutrition, especially for infectious causes such as malaria. Most previous studies investigating the causal relationship between malaria and stunting involved potential confounders controlled via regression-based methods. These studies may were biased by unobserved confounders, including nutritional deficiencies, breastfeeding habits, other infectious diseases, and socioeconomic status[7][8].

Nutritional status is closely tied to the immunological responses to infection, which are other important determinants of the risk and prognosis of infectious disease, as well as being directly influenced by infection[9]. This bi-directional pattern of synergistic interaction, in which a worsening nutritional status negatively contributes to the development and evolution of infection and where infection leads to a worsening of nutritional status, is a crucial aspect of the understanding of an infection's population dynamics and in the establishment of control strategies for these diseases[10]. In theory, any infection increases the risk of undernutrition because sick people eat less, absorb fewer nutrients, lose nutrients (e.g., as a result of diarrhea), and/or have increased nutrient needs due to hypermetabolism. However, as infectious disease, especially malaria and other acute febrile illnesses, are usually acute and ephemeral in nature, if handled correctly, whether they could substantially influence nutritional status is unclear.

PLASMODIUM VIVAX - TRIGGERED UNDERNUTRITION: HOW CAN CLASSICAL CAUSATION CRITERIA HELP US?

Because the first appreciation of causation is based on direct observations, the resulting concept is limited by the scope of those observations, i.e., such a judgment can only be made in the context of all available evidence and must be reevaluated with each new finding[11]. Regarding the *P. vivax*-undernutrition association, relatively few studies have been conducted, using proper methods, to provide adequate evidence of a causal relationship. Here, we discuss these findings, which reveal an association between the two variables beyond what may be attributed to chance. Mimicking Hill[12], *what aspects of that association should we especially consider before deciding that the most likely interpretation is causation?* For that, Hill suggested that the following aspects of an association be considered when attempting to distinguish causal from non-causal associations: 1) strength, 2) consistency, 3) specificity, 4) temporality, 5) biological gradient, 6) plausibility, 7) coherence, 8) experimental evidence, and 9) analogy. These criteria suffer from their origins in inductive reasoning, but their popularity demands a more specific discussion of their practical value[3].

1) Strength. The fact that an association is weak does not rule out a causal connection; however, weak associations are more likely to be explained by undetected biases. The argument that stronger associations are more likely to be causal is reasonable. Only two articles are available in the literature that shows vivax malaria as a risk factor for undernutrition. In Vanuatu, having *P. vivax* malaria within the previous 6-month period was a major predictor of underweight [weight/age, $Z < -2$; adjusted odds ratio (aOR), 2.4; 95% confidence interval (CI), 1.3-4.4; $p = 0.006$] and wasting (weight/height, $Z < -2$; aOR, 2.7; 95% CI, 1.4-5.2; $p = 0.004$) in children, after adjusting for age, sex, season, birth weight, parity, and α-thalassemia genotypes in a multiple logistic regression model[13]. In the Brazilian Amazon, among children who had vivax malaria (aOR, 4.0; 95% CI, 1.4-11.4; $p = 0.008$) and a period of 6-12 months between the last malarial episode and the second nutritional assessment (aOR, 4.4; 95% CI, 1.3-15.3; $p = 0.020$), there was a significant association with increased odds of inadequate growth velocity, after adjusting for the *a priori*-defined variables of age, sex, maternal education, and socioeconomic status[14]. These data support a non-negligible strength of association between vivax malaria and undernutrition in endemic areas.

2) Consistency. In Vanuatu, *Plasmodium vivax* malaria was a major predictor of underweight and wasting in children <5 years of age[13]. In the Brazilian Amazon, among 5-10-year-old children, inadequate growth velocity was associated with vivax malaria episodes, with a period of 6-12 months between the last malarial episode and the second nutritional assessment[14]. These findings are also consistent with the effect of *P. vivax* episodes on the growth of children in Peru[15]. Therefore, consistent findings have been observed in different regions, among different age groups, and using different nutritional outcome assessments, strengthening the existence of an actual effect.

3) Specificity. Causation is likely if a specific population, at a specific site, shows undernutrition when no other likely explanation exists beyond the suspected trigger. The more specific the association between a factor and its effect, the larger is the expectation of a probable causal relationship. Strikingly, this criterion is fragile and invalid, as a general rule. *P. vivax* malaria causes a series of different effects in its carriers and,

undernutrition also has a number of different infectious and non-infectious causes and determinants. In addition, multiple underlying and basic confounders are usually present in areas where malaria is endemic and methodological and analytical constraints are needed to account for all or most of these confounders. The complexity and diversity of the involved factors makes it difficult to establish which, alone or in combination, is sufficient to cause malnutrition.

4) Temporality. In this study, temporality refers to the necessity for vivax malaria to precede undernutrition. As previously stated, three longitudinal cohort studies were conducted in *P. vivax*-endemic areas, using malaria episodes as exposures and anthropometric parameters as outcomes; thus the temporal criterion was fulfilled[13][14][15].

5) Biological gradient. In some cases, the mere presence of a factor can trigger the effect. In others, greater exposures should generally lead to higher incidences of the effect. As such, the biological gradient refers to the presence of a unidirectional dose–response curve. In Vanuatu, during the 6-month period before nutritional assessments, the incidence of *P. vivax* malaria was significantly higher among the underweight and wasting children than among healthy children[13]. Actually, for vivax malaria and undernutrition, the results suggest a monotonic relationship, i.e., more malaria episodes[14] or shorter periods until the nutritional measurement[14][15] lead to greater likelihoods of underweight, wasting, and impaired growth in children. Vivax malaria led to decreases in ponderal velocity of 138.6, 108.0, and 61.0 g/episode over 2, 4, and 6 months, respectively[15]. *P. vivax* can also exist as dormant hypnozoites in the liver, leading to frequent relapses at later times, even months after the primary infection[16]. The impact of vivax malaria remains significant even 6 months after a malarial episode, implying that its growth effect also remained[15]. These observations suggest that the chronic, relapsing nature of *P. vivax* infections may, in highly endemic areas, lead to acute and even chronic undernutrition through cumulative nutritional effects.

6) Plausibility. Older observations point to an association between vivax malaria and chronic relapsing-remitting debilitating fevers associated with hypoproteinemia, edema and weight loss[17]. *P. vivax* is well recognized as a potent stimulator of tumor necrosis factor **alpha** (TNF-α) secretion, resulting in serum levels exceeding those seen in even the most severe forms of *P. falciparum* malaria[18]; pro-inflammatory cytokines also induce both anorexia and cachexia[19]. Although the underlying mechanisms of these occurrences are unclear, they likely involve deleterious catabolic responses associated with the chronic relapsing-remitting inflammation[20][21]. Thus, the role of *P. vivax* in the etiology of undernutrition is biologically plausible.

7) Coherence. The benign characteristics formerly attributed to *P. vivax* infection have been largely dismissed by an increasing number of reports of severe vivax malaria, prompting the need for more thorough and comprehensive characterization of the sequelae resulting from complications[22]. *P. vivax*-associated undernutrition, therefore, seems coherent with current knowledge regarding the virulence of this parasite, increasing the likelihood of a causal effect.

8) Experiment. Hill might have referred to evidence from either animal or clinical studies. Evidence from clinical studies, however, is seldom available for most epidemiologic research questions, and is absent for *P. vivax*-related undernutrition. Similarly, experimental animal evidence describes the effects in different species and usually at exposure levels that are very different from those likely to occur in humans[3]. One possible approach to gaining experimental evidence is to use nutritional status as an outcome in randomized trials of interventions aimed at reducing the incidence of malaria in vivax-endemic areas. In terms of laboratory evidence, little progress has been made to understand pathogenesis and biology of *P. vivax*. Until recently, *P. vivax in vitro* models did not exist, and studying them from human *ex vivo* samples was virtually impossible. Today, non-human primate models are being considered as tools to enable the in-depth study of *P. vivax* biology, especially as it relates to relapsing malaria[23]. However, to our knowledge, information is not yet available regarding *P. vivax*-related undernutrition from non-human primate models. Interestingly, Hill noted that "... *lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations*"[12].

9) Analogy. The diseases most similar to *P. vivax* malaria that can be considered to be analogous are forms of malaria caused by other agents. Indeed, most studies assessing undernutrition as a malarial outcome were conducted in African *P. falciparum*-endemic areas. Previous studies on the association of falciparum malaria and stunted growth delivered inconsistent results, in part due to heterogeneous sample sizes, follow-up times, and exposure and outcome definitions[24]. However, some prospective cohort studies in children showed a risk association between falciparum malaria and subsequent poor incremental weight gains[25], negative impacts on height/age ratios[26][27], and negative impacts on length/age and weight/age parameters[28]. Children who, after initially clearing a falciparum infection, had parasitemia recur within 28 days had a significantly higher propensity of not gaining weight than did children who remained aparasitemic after treatment[29]. Furthermore, a positive association between parasite density and undernutrition was observed[30][31]. With some exceptions[24], these results indicate that acute falciparum malaria contributes to sub-optimal anthropometric development in young children, especially as it relates to acute undernutrition, and may have implications for malaria control efforts in *P. falciparum*-endemic areas.

CONCLUSIONS

Causal inference is a complex process, and arriving at a tentative inference of a causal or non-causal association is a subjective process, limited by the existing evidence. Here, we showed that vivax malaria may contribute to childhood malnutrition, using data that suggest a role for *P. vivax* in the etiology of undernutrition in endemic areas. We continue to seek additional studies that have used larger sample sizes to generate more robust evidence. However, applying classical epidemiology, based on updated principles such as the Bradford Hill criteria, may help reduce the time spent trying to prove causality and allow more interventions to be proposed that

might improve quality of life and decrease morbidity in neglected populations. The complexity and variety of underlying and basic confounders, also common in malaria endemic areas, increase the difficulty of establishing which factor, alone or in combination, provides sufficient evidence of malnutrition causation. The application of modern methods of causal inference in future studies may be useful in this regard. As examples, a combination of Mendelian randomization, using a particular confounder, and matching or instrumental variable regression, is a potential analysis tool for identifying conditions that might be causally related to malaria[7][8]. The public health implications of this association are significant as they allow more comprehensive measurement of the burden of this disease, including any associated conditions.

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