Malaria and Macronutrient Deficiency as Correlates of Anemia in Young Children: A Systematic Review of Observational Studies

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ABSTRACT

Background: Anemia is a leading cause of pediatric mortality and impaired development and is highly prevalent in young children in sub-Saharan Africa. Populations most affected by anemia also often are at high risk for malaria and macronutrient deficiency, conditions that may exacerbate anemia. Due to its multifactorial etiology, anemia presents a significant global health challenge, and successful interventions targeting anemia require a greater understanding of the relative and interacting contributions of malaria and undernutrition.

Objectives: The aim of this study was to assess the associations of malaria and undernutrition, indicated by stunting and wasting, with anemia in young children using a systematic review of observational studies.

Methods: Searches were conducted in MEDLINE and Scopus. Articles were screened and reviewed for inclusion by two reviewers. Studies published after 1990 that measured anemia, *Plasmodium falciparum* malaria, and stunting or wasting in children aged 5 years or under were included.

Findings: Of 620 articles reviewed, 15 studies from 9 countries in sub-Saharan Africa were included. Statistical approaches and anemia measurement varied widely, so synthesis was qualitative. Thirteen studies found that malaria infection was associated with anemia or lowered hemoglobin; in these studies, malaria accounted for more of the variation in anemia than nutritional status. In contrast, only 7 of the 13 studies investigating stunting and 3 of the 6 studies investigating wasting as correlates of anemia observed statistically significant associations at $\alpha = 0.05$. The role of nutrition in anemia may differ by country.

Conclusions: Observational epidemiologic studies consistently demonstrate that malaria is an important correlate of anemia in young children; however, the roles of stunting and wasting and interactions between malaria and nutrition require further investigation. Based on the current evidence, these findings suggest that global health strategies to reduce the burden of anemia should prioritize malaria prevention and support research on alternative causes of anemia that reflect local conditions.

Key Words: anemia, children, malaria, stunting, undernutrition, wasting

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INTRODUCTION

Rationale

Anemia, which is characterized by a reduced red blood cell count, has a complex etiology to which hemoglobinopathies, blood loss, comorbid infections, and nutritional deficiencies can contribute.[1] Due to the multifactorial nature of the disease, efficacious global health interventions designed to reduce the prevalence of anemia may benefit from integrated solutions that recognize the independent and overlapping contributions of comorbid conditions.[2] Although great strides have been made to promote iron fortification to address iron-deficiency anemia in children, such programs are of limited utility in malaria-endemic regions where iron supplementation may increase children's

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vulnerability to infection.[3] Hence, it is important to evaluate the potential roles of alternative modifiable risk factors for young children affected by anemia in these regions.

Viewed independently, anemia, malaria, and undernutrition are all important public health problems. However, they are also linked conditions: the largest burdens of each disease are primarily carried by children residing in sub-Saharan Africa,[4] and all are associated with serious complications, including impaired cognitive and physical development and heightened pediatric mortality.[5-10] Furthermore, it is hypothesized that improving nutritional status and controlling malaria may independently or synergistically decrease children's vulnerability to anemia.[11-16]

Objectives

We aimed to assess malaria and macronutritional status, indicated by stunting and wasting, as correlates of anemia in young children using a systematic review of observational studies.

METHODS

Eligibility criteria

Original research articles were included if the study populations included children aged 5 years or under and measured the following:

1. Any indicator of anemia by hemoglobin or hematocrit measurement;
2. *Plasmodium falciparum* malaria infection with light microscopy or polymerase chain reaction; and
3. Nutritional status by anthropometry (ie, either height-for-age [HAZ] or weight-for-height [WHZ] from which *z* scores are calculated, or both).

Studies published before 1990 were not included because of the improvements and changing guidelines on point-of-care anemia diagnosis due to the HemoCue system,[17] which is now the standard hemoglobin measurement technique in low-resourced settings.[18]

Information Sources

The databases used were MEDLINE (PubMed) and Scopus, using the search strategy described in Figure 1, with the last search performed on December 9, 2014.

Study Selection

Studies retrieved through the database searches were first screened for duplicates and then screened by title and abstract according to the inclusion criteria by two reviewers. Studies included at this stage were reviewed using their full texts and selected based on these inclusion criteria by two reviewers independently. Differences in inclusion decisions at this stage were discussed and reconciled between the two reviewers. The references of these studies were also screened for additional relevant articles, of which the full texts were also reviewed for inclusion.

1) "Protein Deficiency"[Mesh] OR "Protein-Energy Malnutrition"[Mesh]
2) undernutr* OR malnutr* OR undernourish* OR malnourish* OR under-nutr* OR under-nourish*
3) "Nutritional Status"[Mesh] OR "Malnutrition"[Mesh]
4) nutrition
5) 1 OR 2 OR 3 OR 4
6) "Anemia"[Mesh]
7) anemi* OR anaemi*
8) 6 OR 7
9) "Malaria, Falciparum"[Mesh] OR "Malaria"[Mesh]
10) plasmodium falciparum OR p. falciparum OR falciparum
11) malari*
12) paludism*
13) 9 OR 10 OR 11 OR 12
14) 5 AND 8 AND 13

Figure 1. Search strategy for systematic literature review of observational studies.

Summary Measures

Definition for the outcome variable varied across studies (Table 1): World Health Organization (WHO) guidelines for anemia by hemoglobin level[19] were most frequently used, but hematocrit and other cutpoints for hemoglobin also were used. Definitions for exposures also varied. Malaria parasitemia was assessed by polymerase chain reaction[20] in one study and by light microscopy in all others, but definitions of infection ranged from $\geq$1 to $\geq$5000 parasites per microliter. Some studies reported results by degree of malaria parasitemia, but in most *P. falciparum* infection was binary.

The nutritional status indicators assessed in this review, HAZ and WHZ *z* scores, respectively, indicating stunting and wasting at $<$2 SD of the National Center for Health Statistics/Centers for Disease Control and Prevention/WHO International Reference Standard median, were consistent across all included studies.

Odds ratios were extracted from logistic regression models and regression coefficients were extracted from linear regression models. Estimates from multivariate models were used in all but one study that excluded covariates from its final model due to lack of significance, and one that conducted only univariate analyses. Meta-analysis was not considered appropriate due to this lack of consistency in the definitions and types of estimates reported.

RESULTS

Study Selection

Fifteen studies were included from the systematic review as shown in Figure 2.

Study Characteristics and Results

The 15 studies included were all undertaken in sub-Saharan Africa, where this question has the greatest

Table 1. Summary Details of Studies Included in Systematic Review

Country	Study design	Lead author and year	Study population	Outcome (definition)	Adjustment						Effect estimates (95% confidence interval)		
					Age	Sex	Sickle cell	SES	Maternal education	Further adjustment	Malaria	Stunted	Wasted
Burkina Faso	Cross-sectional	Ouédraogo 2008[25]	N = 456; 6-23 mo	Hb (g/dL)							*1-4999 parasites/*µL: b = −0.532 ≥ *5000 parasites/*µL: b = −1.18, P < 0.001	b* = −0.539, *P* < 0.001	b = −0.248, *P* = 0.16
Burkina Faso	Cross-sectional	Müller 2003[15]	N = 709; 6-31 mo	Severe anemia (Hct <24%)	■	■				■	OR, 0.32 (95% CI, 0.07 to 1.39)	*HAZ, increase of 1:*OR, 0.72 (95% CI, 0.60 to 0.86)	*WHZ, increase of 1:* OR, 0.58 (95% CI, 0.43 to 0.78)
Côte d'Ivoire	Prospective longitudinal	Righetti 2013[26]	N = 68, 6-23 mo	Hb (g/dL)	■	■				■	b = −0.15 (95% CI, −0.18 to −0.12)	b = −0.23 (95% CI, −0.48 to 0.01)	
Ghana	Cross-sectional	Ehrhardt 2006[20]	N = 2905; 6-108 mo	Anemia (Hb <11 g/dL)	■					■	OR, 1.40 (95% CI, 1.14 to 1.72)	×	
Ghana	Cross-sectional	Ronald 2006[27]	N = 296; 1-9 y	Anemia (Hb <11 g/dL)	■	■		■		■	OR, 3.92 (95% CI, 2.04 to 7.54)	×	
Ghana, Malawi, Tanzania	Cross-sectional	Siekmans 2014[14]	N = 2404; 24-59 mo	Hb (g/dL)	■	■		■	■	■	b = −0.442 (95% CI, −0.626 to −0.259)	b = −0.333 (95% CI, −0.469 to −0.198)	
Kenya	Cross-sectional	Desai 2005[4]	N = 912; 0-36 mo	Hb (g/dL)	■					■	b = −1.14 (95% CI, −1.14 to −0.87)	b = −0.52 (95% CI, −0.83 to −0.21)	
Kenya	Cross-sectional	Foote 2013[22]	N = 858; 6-35 mo	Anemia (Hb <11 g/dL)	■	■	×	■	■	■	PR* = 1.7 (95% CI, 1.5 to 1.9)	PR = 1.1 (95% CI, 1.0 to 1.2)	PR = 1.2 (95% CI, 1.1 to 1.4)
				Severe anemia (Hb <5 g/dL)	×	×	×	×	×	■	PR = 10.2 (95% CI, 3.5 to 29.3)	PR = 1.6 (95% CI, 1.0 to 2.4)	×
Kenya	Cross-sectional	Halliday 2012[23]	N = 2364; 5-18 y	Anemia (Hb <11 g/dL)	■	■			■	■	OR, 3.68 (95% CI, 2.12 to 6.38)	OR, 1.26 (95% CI, 1.03 to 1.54)	

Kenya	Cross-sectional	Verhoef 2002[16]	N = 318; 2-36 mo	Hb (g/dL)	×	×					b = −1.13 (95% CI, −0.64 to −1.63) *Asymptomatic malaria:* Nonstunted b = −0.86 (95% CI, −0.26 to −1.46); stunted b = −1.64 (95% CI, −0.93 to −2.35)	b = −0.2 (95% CI, −0.07 to −0.34)	b = −0.23 (95% CI, −0.1 to −0.36)
Malawi	Case-control	Calis 2008[21]	N = 1138; 6-60 mo	Severe anemia (Hb <5 g/dL)	■	■			■	■	OR, 2.3 (95% CI, 1.6 to 3.3)		OR, 1.7 (95% CI, 0.9 to 2.9)
Senegal	Case-control	Tine 2012[28]	N = 352; 1-10 y	Anemia (Hb <11 g/dL)	■	■	■				OR, 5.23 (95% CI, 1.1 to 28.48)	OR, 3.37 (95% CI, 1.93 to 5.88)	
Tanzania	Cross-sectional	Mamiro 2011[29]	N = 309; 6 mo	Anemia (Hb <11 g/dL)		×		■	■	■	OR, 1.9 (95% CI, 0.9 to 3.6)	×	
Uganda	Cross-sectional	Osterbauer 2012[13]	N = 600; 4-6 mo	Anemia (Hb <8 g/dL)	■	■		■		■	OR, 5.74 (95% CI, 3.34 to 9.87)		OR, 2.85 (95% CI, 0.85 to 9.54)
Zaire	Cross-sectional	Hedberg 1993[24]	N = 748; 6-59 mo	Anemia (Hct <33%)				■			OR, 3.5, P = 0.0002	OR, 1.8, P = 0.06[†]	

× Indicates variable was measured, but excluded from final model; ■ Indicates covariate was included in multivariate model. Stunting and wasting were defined as HAZ and WHZ, respectively, <2 SD of the NCHS/CDC/WHO International Reference Standard median. Malaria was defined as *Plasmodium falciparum* parasitemia assessed by light microscopy or polymerase chain reaction. HAZ, height-for-age z-score; Hb, hemoglobin; Hct, hematocrit; OR, odds ratio; PF, *Plasmodium falciparum;* PR prevalence ratio; WHZ, weight-for-height z-score.

*b is the multivariate regression coefficient or difference of means as appropriate.

[†]Evaluated in a subset of 342 children.

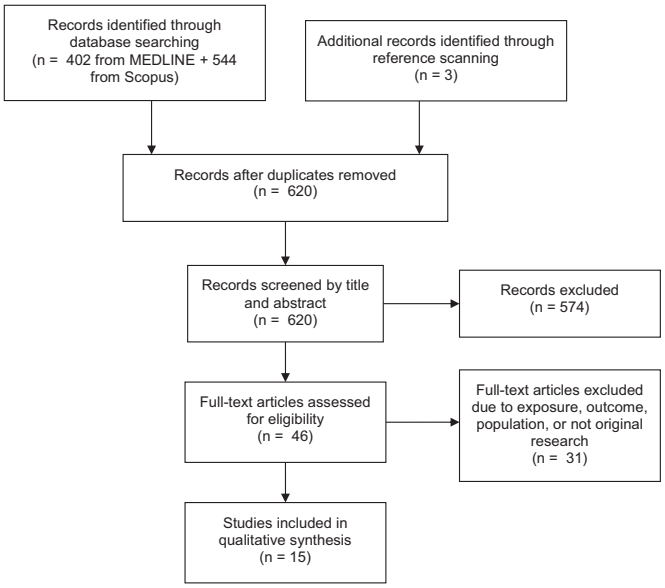

Figure 2. Flow diagram for study inclusion in systematic literature review.

public health importance. Twelve were cross-sectional, 2 were case-control, and only 1 was prospective.

Malaria infection was associated with anemia and lowered hemoglobin; this association had >95% confidence in all but two studies.[4,12-14,20-28] Nutritional status was a less consistent correlate of anemia. Of the 13 studies that investigated associations between stunting (or lowered HAZ) and anemia, 7 found associations.[4,12,14,15,23,25,28] Although stunting was consistently shown to lower hemoglobin across the studies, the magnitude and precision of the estimates varied substantially. Wasting (or lowered WHZ) was investigated in only 6 studies and was associated with anemia in 3.[12,15,22] Effect estimates and levels of adjustment are summarized in Table 1. In all studies that found an association between malaria and anemia, malaria accounted for more of the variation in anemia than either stunting or wasting did. One study investigated interactions between malaria infection and stunting; the interaction was not statistically significant ($P = 0.08$). Most studies adjusted for age, which is an important correlate of anemia. Sex and socioeconomic status were also commonly included in models; a variety of other covariates were included as described in Table 1, leading to substantial heterogeneity in the levels of adjustment.

The prevalence of the exposures (ie, malaria, stunting, and wasting) also varied across studies, as shown in Table 2.

DISCUSSION

Summary of Evidence

The evidence identified through the systematic review suggests that malaria infection and, to a lesser degree, macronutrient deficiencies as manifested by stunting and wasting are associated with anemia in young children. The direction of effects of all exposures (ie, malaria, stunting, and wasting) on anemia was consistent across settings, designs, and study sizes.

The association of malaria and anemia was robust to malaria transmission context and prevalence, urban or rural setting, and country. The consistency and relatively large effect sizes of the statistically significant associations between malaria and anemia lends credence to the claim that malaria is an important predictor of anemia in young children. This association was observed across a range of malaria prevalence from 3.12%, in a Senegalese sample that had low precision but a large effect size,[28] to 81.6%, in a Ghanaian rainy season sample[20] (Table 2). One study that investigated various levels of malaria parasitemia suggested a dose-response relationship between parasite load and lowered hemoglobin.[25]

Two studies[15,29] found no statistically significant associations between malaria and anemia. Whereas, in a Tanzanian population,[29] the prevalence of malaria was found to be 48%, which is similar to other studies, the prevalence of malaria in one study in Burkina Faso was low at 6.25%.[15] In addition to the low prevalence of malaria, which decreased the precision of the estimate, measurement error may have been introduced as severe anemia was measured within a 10-day window following blood smear measurement rather than simultaneously. In contrast, the lack of association in the study in a Tanzanian population is likely due to a lack of statistical power; this was the second-smallest study included ($N = 309$) and the P value for malaria in the multivariate model was of borderline significance. Although iron deficiency and socioeconomic factors were associated with anemia in multivariate models, malaria was associated with anemia in univariate analysis (odds ratio, 2.8; 95% confidence interval, 1.5 to 5).[29]

The consistency of these observational results underscores the importance of malaria; as one study argued, interventional studies may underestimate the importance of malaria because malaria control measures such as either insecticide-treated net distribution[14] and use or intermittent preventive treatment (IPT) with sulfadoxine-pyrimethamine are complex to implement and may control malaria poorly.[16,30] From the articles in this review, no effect was found on anemia from access to IPT in a sample of Senegalese children,[28] and no effect was found on anemia from children sleeping under an insecticide-treated net.[13] Rather than drawing into question the role of malaria in determining anemia, which both studies' observational results confirmed, this may indicate failures in implementation of these malaria control measures.

There is less consistent evidence to suggest undernutrition as measured by stunting and wasting is associated with anemia; 8 studies found significant associations between stunting or wasting and anemia. There were no systematic differences in level of adjustment or type of covariates in studies that detected associations between undernutrition and anemia, although they were mainly

conducted in Kenya[4,12,22,23] and Burkina Faso.[15,25] There were no systematic differences in the prevalence of malaria, stunting, or wasting in these studies (Table 2), but further research might investigate other contextual differences (eg, malaria control programs, other infections, supplementation, or treatment practices) in malaria and undernutrition.

Using the cutpoint of <2 SDs of the reference median, a prevalence for both stunting and wasting of 2.5% is expected in a healthy population. Although stunting prevalence was overall much higher than this, many studies had low wasting prevalence, from 0% to 5%,[12-14,22,27,29] possibly limiting power to detect any association of wasting with anemia (Table 2). If wasting has low prevalence, its public health importance as a risk factor is likely also low, regardless of its ability to predict anemia, and stunting is likely to be a better indicator of any associations that exist between undernutrition and anemia.

Other infections and micronutrient deficiencies also can be associated with stunting. Studies that investigated other infections, including bacteremia and hookworm, A and B vitamin deficiencies, and genetic factors had varying results; genetic factors and inflammation or infection were associated with anemia in two studies.[21,22] One study found associations between vitamin A and B_{12} deficiencies and anemia, but no folate deficiency in the population,[21] whereas another study found no association with vitamin A deficiency in a multivariate model,[22] and only a univariate association with vitamin A deficiency was found in a third study.[26] Iron is also a complex issue. In two of the studies included in this review that also assessed iron status, iron deficiency was associated with increased odds of anemia, but in a study that used the stricter cutoff of severe anemia, defined as hemoglobin <5g/dL, iron deficiency was protective (OR, 0.4; 95% CI, 0.2 to 0.6).[21]

Overall, this review found little evidence testing the hypothesis that macronutrient deficiency could interact with malaria to synergistically cause anemia. In the one study that investigated the interaction in a cohort of 318 children, there was evidence of borderline significance ($P = 0.08$) for effect modification by stunting on the association between malaria and anemia, but few conclusions can be drawn in the absence of more robust confirmatory evidence.

The studies included in this review underscore the point that anemia is multifactorial and likely context-dependent. Where covariates such as age, urban or rural location, socioeconomic status, and maternal education were measured, they tended to be associated with anemia. Other local conditions, such as elevation and school feeding programs, were less frequently measured but important in one study.[23]

Table 2. Malaria, Stunting, and Wasting Prevalence in Studies Included in Systematic Review

Lead author and year	Country	Prevalence, N (%)		
		Malaria	Stunted	Wasted
Ouédraogo 2008[25]	Burkina Faso	240 (52.6)	93 (20.4)	117 (25.8)
Müller 2003[15]	Burkina Faso	34 (6.25)	*Mean HAZ* −1.5 (June), −1.6 (Dec)	*Mean WHZ* −1.2 (June), −1.3 (Dec)
Righetti 2013[26]*	Côte d'Ivoire	*Mean log parasite load* 16.2 (95% CI, 5.97 to 41.3)	—	—
Ehrhardt 2006[20]	Ghana	*Dry season* 1570 (74.5) *Rainy season* 1729 (81.6)	683 (23.5)	423 (14.6)
Ronald 2006[27]	Ghana	75 (25.3)	42 (14.2)	16 (5.1)
Siekmans 2014[14]†	Ghana	52 (28.1)	180 (32.8)	49 (8.92)
	Malawi	239 (20.9)	645 (56.3)	41 (3.57)
	Tanzania	82 (11.5)	456 (64.2)	19 (2.68)
Desai 2005[4]	Kenya	601 (66.6)	213 (24.4)	54 (6.1)
Foote 2013[22]	Kenya	276 (32.5)	252 (29.6)	28 (3.3)
Halliday 2012[23]	Kenya	311 (13.0)	603 (25.2)	—
Verhoef 2002[16]	Kenya	56 (17.6)	123 (38.7)	15 (4.7)
Calis 2008[21]	Malawi	547 (48.1)	—	95 (8.4)
Tine 2012[28]	Senegal	11 (3.12)	136 (38.64)	33 (9.38)
Mamiro 2011[29]	Tanzania	148 (48.0)	108 (35.0)	3 (1.0)
Osterbauer 2012[13]	Uganda	122 (20.3)	60 (10.0)	18 (3.0)
Hedberg 1993[24]	Zaire	166 (22.2)	66 (19.3)	—

Stunting and wasting were defined as HAZ and WHZ, respectively, <2 SDs of the NCHS/CDC/WHO International Reference Standard median. Malaria was defined as *Plasmodium falciparum* parasitemia assessed by light microscopy or polymerase chain reaction. HAZ, height-for-age z-score; WHZ, weight-for-height z-score.

*Geometric mean of natural log parasite load per microliter reported for end-of-study survey; no difference between first and last survey by Wilcoxon signed rank test. Multivariate model adjusted for survey number. Prevalence not reported.

†Prevalence aggregated across 2000 and 2004 samples; only statistically significant differences in Ghana (37.2% to 29.1%) and Tanzania (65.5% to 53.2%) for stunting prevalence from 2000 to 2004, and in Malawi for malaria prevalence (31.8% to 13.4%). Multivariate model adjusted for study year.

Limitations of the Evidence

There were several important limitations of the studies included in this review, which can be used to inform the design of future investigations. There were no small studies that found null or small effects, indicating that publication bias may exist in this literature. One case-control study used hospital controls[21] which can introduce Berksonian selection bias, a type of bias to which cross-sectional studies, representing the majority of studies included, are unlikely to be susceptible. Classifying children as anemic or not, instead of conducting analyses

using continuous hemoglobin variables, also may have decreased the power of most studies included to detect effects. Additionally, some studies applied other criteria to the outcomes (eg, asymptomatic malaria and anemia were used in one study[12], severe anemia was used in 3 others[13,15,21]), and some studies were excluded because they used malarial anemia or iron-deficiency anemia as the outcome and thus were unable to investigate separate associations of malaria and nutrition with anemia. Some studies reported population attributable risks,[24,27] which are inappropriate to their cross-sectional design and should thus be interpreted with caution; the use of prevalence ratio is more interpretable for cross-sectional designs.[22] Strengths of the studies included the large number of potential confounders measured and included in the models, which minimized the effect of residual confounding, the relatively large sample sizes of most studies, and the geographic distribution of evidence, which included both east and west African countries.

Limitations of the Review

This review was limited by its lack of a quantitative synthesis due to incomparability of effect estimates. Comparison was also impeded by the fact that not all studies presented effect-size estimates for all 3 exposures (malaria, stunting, and wasting) and because information about micronutrient supplementation and deficiency was available for only a small subset of studies. Furthermore, this review did not investigate associations with additional parasitic strains, such as *P. vivax*, which is of epidemiologic importance in non-African settings. Additionally, seasonality is important in malaria and may influence the relative importance of malaria and nutritional factors in determining anemia, but this review did not aggregate or consider season of measurement. Original research would have the capacity to do so.

Future Research

Further research should also investigate nutrition and malaria in a wider context. Specifically, research and policies that only address macronutrition are unlikely to succeed in understanding and addressing the complex effects of macro- and micronutrition on anemia. Furthermore, given the importance of genetic, demographic (ie, age) and contextual (ie, socioeconomic status and rural location) factors in the studies included in this review, future research should either measure these covariates rigorously, or randomize interventions to participants with various characteristics. Salient issues for future research include between-country and between-context differences in the etiology of anemia, the role of other infections (eg, helminths), unconfirmed interactions between malaria and nutrition, and links between macro- and micronutrition, malaria, and anemia. Use of more sophisticated malaria data, such as in a recent study using modelling of prevalence in holoendemic regions, could be used as a predictor for malaria-associated morbidity and to target interventions,[31] and seasonality and associations with other species of malaria should be investigated.

CONCLUSION

Anemia control is important to support healthy child development,[5,6] decrease mortality,[7,21,25] and mitigate the prevalence of transfusions in countries where blood supplies are frequently contaminated with HIV and other infectious agents. Governments hoping to reduce the burden of anemia in young children must make resource-allocation decisions based on available scientific evidence on the importance of the known risk factors for anemia. This review adds to the literature on anemia control by emphasizing the consistency of malaria as a correlate of anemia in young children across various contexts. It also underscores the complexity of nutrition's role in anemia by showing that macronutritional status, although commonly associated with anemia, is neither as consistent nor as strongly associated with anemia as is malaria.

Funding silos frustrate the control of a multifactorial condition like anemia. Research that investigates multiple risk factors for anemia, such as that presented here, is a valuable tool in evaluating the importance and prioritizing among various interventions and further research efforts. This evidence-based strategy is preferable to a disease-specific intervention approach in terms of outcomes and cost-effectiveness[6]; however, all targets of integrated programs should be investigated for their importance as risk factors in order to maximize effectiveness and minimize harm. Consistent risk factors for anemia, including malaria infection, might form the basis of an integrated program onto which further context-specific interventions, such as macro- or micronutritional supplementation, could be added if they are supported by robust evidence.

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