Published in final edited form as:
Am J Trop Med Hyg. 2007 December ; 77(6 Suppl): 88–98.

EPIDEMIOLOGY OF PLASMODIUM-HELMINTH CO-INFECTION IN AFRICA: POPULATIONS AT RISK, POTENTIAL IMPACT ON ANEMIA AND PROSPECTS FOR COMBINING CONTROL

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Abstract

Human co-infection with Plasmodium falciparum and helminths is ubiquitous throughout Africa, although its public health significance remains a topic for which there are many unknowns. In this review we have adopted an empirical approach to investigating the geography and epidemiology of co-infection, and associations between patterns of co-infection and haemoglobin in different age groups. Analysis highlights the extensive geographic overlap between P. falciparum and the major human helminth infections in Africa, with the population at coincident risk of infection greatest for hookworm. Age infection profiles indicate that school-age children are at the highest risk of co-infection, and re-analysis of existing data suggests that co-infection with P. falciparum and hookworm has an additive impact on hemoglobin, exacerbating anemia-related malarial disease burden. We suggest that both school-age children and pregnant women – groups among the highest risk of anemia - would benefit from an integrated approach to malaria and helminth control.

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Keywords

Malaria; helminths; hookworm; co-infection; anemia; epidemiology; disease burden; disease control; Africa

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INTRODUCTION

Malaria poses an enormous public health burden and more than 75% of the global clinical episodes due to *Plasmodium falciparum* each year are concentrated in Africa.1 Across the continent, a number of helminth species share the same spatial extents as *P. falciparum*. The most ubiquitous of these are the soil-transmitted helminths (STH: *Ascaris lumbricoides*, *Trichuris trichiura,* and hookworms), which infect more than a third of the continent's population infected at any one time.2 The schistosomes, *Schistosoma haematobium* and *S. mansoni*, are also endemic throughout the continent, but generally have a much more focal distribution than STH species.3 In Africa, the overall prevalence of *Wuchereria bancrofti*, which causes lymphatic filariasis (LF), is low4, but the disease continues to be of considerable local importance in endemic foci. Finally, onchocerciasis, caused by *Onchocerca volvulus*, is widely distributed throughout the continent.5

Spatial congruence of both *P. falciparum* and different helminths remains poorly defined. Preliminary analyses however, suggest that as many as a quarter of African schoolchildren may be coincidentally at-risk of *P. falciparum* and hookworm.6 This spatial coincidence of risk between these two parasite populations would suggest that co-infection is extremely common although the public health significance of polyparasitic infection remains a topic for which there are many unknowns. For example, although we know that helminth infections elicit a potent, highly polarized immune responses characterized by elevated T-helper cell type 2 (Th2) cytokine and Immunoglobulin(Ig)E production,7 it is unclear whether these responses may modulate human immune responses to malaria and therefore alter susceptibility to clinical disease.8 Similarly, although malaria and helminth infections are known aetiological factors in tropical anemia,9-11 the extent to which their combined presence might interact to further enhance the risk of anaemia is poorly understood. Finally, although the relevance of an integrated, non-disease specific approach to controlling childhood anemia is an increasingly recognized strategy12, following a general move toward integrated disease control programmes,13, 14 the public health evidence base for combined malaria and helminth control requires better definition.

Two recent reviews have focused on either the epidemiological 15 or immunological 8 evidence on plasmodium-helminth interactions. In contrast, this paper quantitatively investigates the geography and epidemiology of co-infection and its potential impact on anemia, as well as the exploring the wider implications of co-infection for disease control in Africa.

PREDICTED PATTERNS OF CO-DISTRIBUTION

The large-scale distributions of parasitic diseases are governed by a number of environmental factors, principally temperature and humidity. We have previously used a combination of temperature, rainfall and altitude to predict the continental distribution of each of the major STH species.2 These models suggest that the prevalence of *A. lumbricoides and T. trichiura* is greatest in equatorial, central and west Africa, eastern Madagascar and southeast Africa, whereas hookworm is more widely distributed across the continent. Other workers have used climate-driven Fuzzy logic models to define the suitability for stable malaria transmission across Africa16, and previous estimations 17, 18

classify transmission conditions into four classes: zero risk, marginal risk, acute seasonal risk and stable risk. Combining these different spatial models has previously allowed the estimation of the co-distribution of *P. falciparum* and hookworm and the school-age populations at risk of coincident infection.6 Here we extend this approach to quantify the populations at risk of infection with both *P. falciparum* and each of the major STH species. In areas of stable endemic malaria transmission between 17.8-32.1 million children aged 5-14 years are estimated to be at risk of co-infection with *P. falciparum* and different STH species, with the risk greatest for hookworm (Table 1). Between 5.8-9.6 million and 1.6-3.4 million children at risk of co-infection in areas of acute marginal seasonal transmission and marginal transmission, respectively. This analysis indicates that the coincidental malaria-STH at-risk population is greatest for hookworm than either *A. lumbricoides* or *T. trichiura*. Schistosomiasis has a more focal distribution due to spatial heterogeneities in snail dynamics and human behaviour3, making the prediction of co-distribution with malaria more difficult to assess. Finally, many of the areas endemic for LF and onchocerciasis are also affected by malaria,19 although this remains to be reliably quantified.

EPIDEMIOLOGY OF CO-INFECTION

Patterns of single parasite species infection of STH or *P. falciparum* have been well documented during classical epidemiology. Both types of parasites exhibit marked age-dependency in infection patterns. Age-stratified epidemiological studies indicate that the prevalence of asymptomatic *Plasmodium* infections increases in early childhood, beginning to decline with the gradual acquisition of immunity. The precise rate and age at which immunity is acquired is exposure dependent, but in areas of stable transmission infections in adulthood are generally low (Figure 1). In contrast, the prevalence of STH and schistosomiasis infections increases throughout childhood to a relatively stable plateau or show a slight decrease in adulthood. The highest prevalence of LF generally occurs during adulthood, though there has been increasing appreciation of LF as an important public health problem among children and adolescents.20 In contrast to such characteristic age dependency, age-specific patterns of *O.volvulus* show strong variation according to locatities.21

Helminths have an over-dispersed distribution, with most individuals harbouring few or no worms and the majority of the worm population found in a minority of individuals 22; it is within this group that most of the morbidity occurs. Similar patterns of over-dispersion are also evident for *P. falciparium* infections: recent modelling of parasite prevalence and the basic reproduction rate of infection suggests that 20% of children in a community receive 80% of new infections in a community.23 Both malaria and helminth infections have a tendency to cluster within certain families and households.24, 25

In contrast to the well-characterised patterns of single parasite infections, we know surprisingly little about the patterns and risk factors of co-infection within communities. The occurrence of co-infection will depend on (i) the overall prevalence of individual species and (ii) the degree of association between different species. If infection with *P. falciparum* and helminths are independent then occurrence of co-infection is simply determined by the relative frequency of individual species. Thus, the age patterns of co-infection will depend on the age-specific prevalence rates as predicted by simple probability. However, if co-infection is either synergistic or antagonistic then occurrence of both parasites would be significantly different from that predicted by individual chance encounters with either infection. Such associations may arise due to biological associations, whereby the presence of one species promotes or inhibits the establishment and/or survival of the second species, potentially through immune modulation.8 Alternatively, co-infection may reflect concurrence of common socio-economic and/or environmental risk factors promoting

survival of both species.15, 26 At present, there are too few studies able to disentangle the relative importance of different risk factors for co-infection and detailed epidemiological studies are clearly warranted.

However, on what we currently know about the epidemiology of co-infection, it is suggested that school-age children, rather than pre-school children or adults, are most at-risk of plasmodium-helminth co-infection (Figure 1), and thereby at greatest risk of the consequences of co-infection. The next section provides a brief review of the immunological consequences of co-infection, before turning to the impact of co-infection on hemoglobin levels.

IMMUNE CONSEQUENCES OF CO-INFECTION

The successful resolution of *Plasmodium* infection requires a coordinated succession from a T-helper cell type 1 (Th1) to a Th2 type response, and anything that upsets the timing or balance of this process can lead to chronic or severe infection.27 The Th2-skewed immune profile and profound cellular hyporesponsiveness induced by chronic helminth infection7 might therefore be expected to affect the course of *Plasmodium* infection. This hypothesis has led researchers to investigate the interactions between *Plasmodium* and helminth infection. However, limited observational studies so far have provided conflicting accounts of the effects of chronic helminth infection on host immune responses to malaria. Early studies suggested that *Ascaris lumbricoides* infection might be protective against malarial disease,28, 29 in contrast to several later reports, which suggested that STH infections may increase the risk of malaria infection. 26, 30-33 Conversely, a potential protective effect on malaria of light schistosome infection has been reported in Senegal and Mali.34, 35 Other studies have noted a difference in the development of severe malaria between helminth-infected and uninfected individuals, with several studies from Thailand suggesting a protective effect for *A. lumbricoides* infection on the risk of cerebral malaria and acute renal failure,36-39 although again this is in contrast to a study in Senegal, which suggested a positive association between infection with *A. lumbricoides* and the occurrence of severe malaria.33 Thus, epidemiological observations now suggest a range of scenarios in which helminth infections may increase susceptibility to *Plasmodium* infection but may also under certain circumstances protect against severe malaria.8 The potential immuno-regulatory mechanisms by which helminths may alter immune responses to malaria are summarized in Figure 2. Despite the biological plausibility of synergism and antagonistism and the somewhat contradictory evidence15, the precise relationship between co-infection and clinical malaria continues to remain difficult to empirically determine, and definitive studies are urgently needed to resolve the issue.

Figure 2 also illustrates the possible mechanisms by which malaria and helminths may cause anemia. The next section expands on these mechanisms and assesses the epidemiological evidence on the potential impact of co-infection on hemoglobin levels.

IMPACT OF CO-INFECTION ON ANEMIA

Anemia is one of the most widespread and common health condition afflicting individuals living in the tropics, and in Africa contributes to 23% of nutrition-related disability-adjusted life years.40 The consequences of anemia are particularly severe for children and pregnant women.12, 41 Chronic anemia during childhood is associated with impairments in physical growth, cognition and school performance,42 while severe anemia accounts for up to half of the malaria attributable deaths in children under five. 43, 44 Maternal anemia is associated with low birth weight and increased maternal morbidity and mortality.38 While the etiology of anemia is complex and multi-factorial in origin, parasitic diseases, including *P.*

falciparum and helminth infections, have long been recognised as major contributors to anemia in endemic countries.

Recent meta-analyses of malaria intervention trials among African children provide compelling evidence that both symptomatic and asymptomatic malaria contributes substantially to anemia inendemic regions.43, 45 Malaria contributes to reduce hemoglobin concentrations through a number of mechanisms, principally by destruction and removal of parasitized red cells and the shortening of the life span of non-parasitized red cells, and decreasing the rate of erythrocyte production in the bone marrow.46 Some of the mechanisms that cause anemia during malaria are associated more with the acute clinical states (e.g. hemolysis or cytokine disturbances), whereas chronic or repeated infections are more likely to involve dyserythropoiesis.9 Data among Ghanaian schoolchildren suggest that hemoglobin concentration was 9 g/L lower among children with asymptomatic *P. falciparum* infection than children uninfected.47 Although this finding cannot be extrapolated to all settings, these results suggest that asymptomatic parasitaemia may be associated with a marked reduction in hemoglobin concentration among older children who are also at highest risk of helminth infection.

The effects of infection with a single helminth species on the risk of anemia are well documented, with risk correlated with infection intensity. 11, 48, 49 A recent study among Filipino schoolchildren highlights how even low-intensity multiple helminth infections enhance anaemia risk.50 Hookworm causes iron deficiency anemia through the process of intestinal blood loss.10 Schistomes also cause anemia by chronic blood loss, as eggs penetrate the wall of the bowl (in intestinal schistosomiasis) and the urinary tract (in urinary schistosomiasis).11 Like malaria, anemia due to schistosomes can additionally arise from destruction of red blood cells and/or dyserythropoiesis. *Ascaris lumbricoides* and *Trichuris trichuria* typically have little impact on iron status.51

Based on the distinct mechanisms by which malaria and hookworm and schistosomes reduce hemoglobin levels, it can be speculated that their combined presence might interact to enhance the risk of anemia. However, little is known about the impact of co-infection on anemia among different age groups. We have approached this paucity of data by re-analysing available data from Kenya to investigate the association between co-infection and hemoglobin levels (Figure 3). Data for pre-school children indicate that co-infection with *P. falciparum* and heavy hookworm is associated with significantly lower hemoglobin concentration than single infections with either *P. falciparum* or hookworm (Figure 4a). Among schoolchildren, hemoglobin is 4.2 g/L (95% CI: 3.1-5.2 g/L) lower among children harbouring co-infections than single species infections (Figure 4b). In contrast, no significant difference was observed among pregnant women; although both malaria and hookworm alone had a significant impact on hemoglobin levels (Figure 4c). Although these data are suggestive of an additive impact of co-infection on anemia in certain age groups, it should be noted that such associations may be confounded by socio-economic, genetic and nutritional factors, and that the effects of co-infection may vary by malaria and helminth transmission intensities.52 Consequently, randomized controlled trials of combining malaria- and helminth-specific interventions aimed at establishing the contribution of co-infection on anemia should be conducted in a range of transmission settings.

In the absence of further data on the effects of co-infection on anemia, the significance of these re-analysed data must be treated with caution but should not be ignored either. Overlooking the impact of co-infection may underestimate the disease burden of malaria. For young children, co-infection may be relatively unimportant since, although the impact of co-infection on hemoglobin levels is extremely marked, co-infection occurs relatively infrequently (only 3.5% of pre-schoolers harboured both heavy hookworm and *P. falciparum*

infection). Among school-age children the picture appears different however: 35.2% of school-age children in the Kenyan study harboured both heavy hookworm and *P. falciparum* infection. On the assumptions that these data are representative, the impact of co-infection on anemia may be associated with a significant disease burden among African school-age children in areas of high parasite transmission. In numerical terms, up to 32 million African school-age children in areas of stable malaria transmission may be at risk of heavy hookworm and *P. falciparum* infection, and thus at enhanced risk of anemia. 6 The situation in settings with low parasite transmission or adequate nutritional intake is currently unknown and merits exploration. The next section discusses potential approaches to combining malaria and helminth interventions aimed at reducing the anemia-related disease burden associated with co-infection.

COMBINED CONTROL

Several effective malaria control interventions currently exist, including residual house spraying, insecticide-impregnated materials (particularly bed nets), and antimalarial drugs. Increasing political and financial support for malaria control, as well as renewed emphasis on population-based anthelmintic treatment,14 makes a combined malaria-helminth approach to control timely. Although the appropriateness of different intervention strategies will depend on a complex of interacting factors that determine the epidemiology of infection and availability of delivery mechanisms, there exist multiple potential for combining malaria control with helminth control (Table 2).

Infants and pre-school children

While early diagnosis and prompt treatment is a vital element of malaria control,53 chemoprophylaxis and insecticide-treated nets (ITNs) have been shown to be highly effective at reducing malaria-related mortality and morbidity.54-56 A promising new alternative malaria control strategy is intermittent preventive treatment in infants (IPTi).57 Here, treatment doses of sulphadoxine/pyrimethamine (SP) are delivered to infants, irrespective of infection status, at the time of routine vaccination during the first year of life. Additionally, studies in west Africa have demonstrated that seasonal IPT could be an effective malaria prevention strategy among children under five years of age in areas of seasonal malaria transmission,58, 59 but further investigation is required to determine whether this is a practical approach to malaria control.60, 61 In terms of the impact of IPTi on anemia, a trial among Tanzania infants found a 50% protective efficacy against severe anemia.62 Among Ghanaian infants, IPTi was associated with a significantly higher mean packed cell volume at 12 months of age, but was associated with slightly lower volumes at 18 months.63

Regarding helminth control among pre-school children, the benefits of deworming are increasingly appreciated. For example, recent evidence from Zanzibar indicates that anthelmintic treatment significantly reduced the prevalence of anemia and stunting among pre-schoolers who received mebendazole every three months for a year.64 On the basis of available evidence on the effectiveness of treatment and the safety of providing to young children, WHO now recommends in areas of high helminth prevalence to provide anthelmintic treatment to children from the age of 12 months.65, 66 Thus, anthelmintic treatment could potentially be co-administered with IPT to children aged one to five years in areas of seasonal malaria transmission. Based on current guidelines, deworming is unable to be provided as part of IPTi activities.

School-age children

The delivery of malaria chemoprophylaxis to schoolchildren through schools was widespread in Africa during the 1950's and 1960's, and resulted in significant reductions in parasitaemia and rates of anemia and clinical malaria attacks.45, 67 However, regular chemoprophylaxis in malaria-endemic countries proved to be unsustainable, largely due to problems in drug distribution and financing and concerns about the potential emergence of drug resistance.68 Today there is a renewed interest in the potential of the education sector to address the impact of malaria on school-age children.69, 70 A recent study of the impact of insecticide (permethrin)-treated bed nets (ITNs) on the health of adolescent schoolgirls in western Kenya found that ITNs were associated with an increase in hemoglobin concentrations (0.34 g/dL (95% CI = 0.02, 0.66)).71 A study in Tanzania demonstrates the effectiveness of teachers in recognizing and treating malaria in school children,72 and a study in Malawi demonstrated the effectiveness of presumptive treatment in reducing malaria-related mortality among schoolchildren where teachers were trained to use “first aid kits” to dispense SP treatment to symptomatic children.73

IPT may also prove a valuable approach in older children in preventing malaria-related anemia. A trial was recently completed among schoolchildren in a high malaria transmission area of western Kenya evaluating the effect of IPT using SP combined with amodiaquine on children's hemoglobin concentrations and their ability to concentrate in class, whereby children were provided with a curative treatment dose every term during the school year, regardless of infection. Preliminary results indicate that IPT almost halves (protective efficacy 55%, 95% confidence interval [CI]: 20-74%) the occurrence of anaemia and reduces malaria parasitaemia by 90% (95% CI: 82-95%) (Clarke and others, unpublished data). Future work will address the effectiveness of the approach in a range of transmission settings and the operational feasibility of integrating the approach into current school health programs, including provision of IPT by teachers.

In contrast to the operational uncertainties and absence of guidance as to good practice for malaria control in schools, global efforts are already underway to control helminth-related morbidity among school-age children through the combined delivery of praziquantel to treat schistosomiasis and benzimidazole anthelmintics, albdendazole and mebendazole, to treat STH infections. Because the most intense helminth infections and related illnesses occur at school age 74, 75 and infection can have adverse consequences for health and development, 76 many of which is rapidly reversed by treatment, school age children are the natural targets for treatment. In addition, school-based treatment delivery programs offer several cost advantages because of the use of the existing school infrastructure and the fact that schoolchildren are accessible through schools.77

Thus, school-based deworming programmes may provide a possible entry point for combined delivery of IPT and anthelmintics, or at least a way of sharing resources to do so, with limited increase in operational costs. Combined school-based parasite control is not new, however, and many useful lessons can be learned from past experiences.78 Health promotion activities and teaching within schools to encourage good hygiene practices and awareness of malaria prevention methods, such as the use of sleeping under an insecticide-treated net, will help support and maintain health gains.

Pregnant women

The current recommended control strategy for malaria during pregnancy in areas of stable transmission is IPT with SP, given during the second and third trimester,66 which provides benefits in terms of reduced rates of maternal anemia 79 and malaria morbidity.80, 81 The use of ITNs, which have a well-documented beneficial impact on pregnancy outcomes,82 is

also advocated. Although screening and treatment for hookworm infection in pregnant women is recommended,83 there are surprisingly very few published studies reporting the impact of deworming on maternal health or pregnancy in Africa. Trials among pregnant women in Sierra Leone84 and in Peru85 show that deworming resulted in increased hemoglobin concentrations, and a study in Nepal found that deworming resulted in improvements in maternal iron status, birth weight and perinatal survival.86 Further investigation of the benefits of deworming among African pregnant women is clearly needed. Although co-infection was not found to be associated with lower hemoglobin among Kenyan pregnant women (Figure 4c), the detrimental effects of malaria and hookworm alone – together with the potential impact of schistosomiasis in pregnancy87 – warrants the evaluation of the combined use of IPT with SP and anthelmintic treatment. The potential additive benefits of combining interventions targeted at anemia is illustrated by a study in Sri Lanka which showed that mebendazole given in combination with iron-folate can improve hemoglobin and iron status more than iron-folate alone.88

Community-based control

ITN distribution and residual house spraying are the main community-based malaria control strategies. In the more rural areas Africa, the same *Anopheles* mosquito species transmit both LF and malaria; in most urban and semi-urban areas, *Culex* spp. mosquitoes are the major vectors for *W. bancrofti*. Pilot studies indicate that ITNs can impact on vector biting densities of both *Anopheles* spp. and *Cx. quinquefasciatus* and on overall transmission of *W. bancrofti*.89, 90 For this reason, it has been suggested that the global LF programmes lends itself particularly well to linkage with malaria control programmes in areas co-endemic for LF and malaria.19

The cornerstone of onchocerciasis control is larviciding of *Simulium* (blackfly) vector breeding grounds and mass drug administration with ivermectin.5, 91 Since 1995, the African Programme for Onchocerciasis Control has implemented community-directed treatment (CDT) with ivermectin, whereby communities themselves appoints local drug distributors.91CDT has also been a feature of the Global Programme to Eliminate LF, whereby communities are treated with albendazole and ivermectin in areas where onchocerciasis is endemic and albendazole and diethylcarbamazine (DEC) elsewhere.92 The CDT strategy is increasingly being used as platform to combining other community-based health interventions, including malaria interventions.19 Such linkage can help maintain high coverage levels achieved through onchocerciasis and LF CDT-based control. For example, recent experience in Nigeria suggests that integrated distribution by community volunteers of anthelmintics against LF and onchocerciasis, as well as ITNs, resulted in an increased net uptake.93 These observations provide early indication of the feasibility of ITN distribution through a mass treatment campaign for helminths.

PROPOSED RESEARCH AGENDA

If there was a move toward a combined strategy to malaria-helminth control there is a need to broaden the scope of research. Clearly the epidemiology of co-infection must be better studied before appropriate recommendations for the appropriate epidemiological setting can be made. The relevance of different parasite-specific interventions will vary according to different transmission intensity conditions.94 For example, IPTi may only be appropriate in areas of stable or seasonal malaria transmission, but not areas of low transmission. Moreover, whether iron supplementation should be withheld in young children is crucially dependent on understanding of the relative risk of iron deficiency and the rate of exposure to malaria, such that recommendations for iron supplementation cannot be based on a limited number of studies but need to be tailored to the nutritional status of the population and the intensity of malaria transmission.95 Finally, the impact of different mixes of interventions

may depend on the intensity of malaria and helminth transmission – a single approach to combined control is highly unlikely. To guide rational control a number of key issues need to be empirically investigated in a range of transmission and operational settings. As a first effort, we propose the investigation of the following key areas.

First, to better define the consequences of co-infection related anemia requires more detailed analysis of empirical data on hemoglobin concentrations among different population groups to investigate the relationship between malaria-helminth co-infection on hemoglobin and iron deficiency anemia. The recently launched studies of IPT can potentially be combined with deworming to provide a more powerful platform to quantity the consequences of co-infection on anemia more precisely. There is also a clear need to look at mechanisms of this process when confronted with a co-infected individual. Therefore measurements of intestinal blood (fecal protoporphyrin), shortened RBC half life, iron binding capacity, splenic sequestration, dyserthyropoiesis should be examined in the polyparasitized, it may be more than additive. Such work is important to better define the contribution of co-infection to public health burden in Africa and would also allow for a realistic framework to understand how to target intervention needs, as well as, provide a rubric against which to measure progress toward national and international public health goals.

Second, to help identify priority areas for combined control, there is a requirement to delineate and understand the spatial overlap and co-endemicity of malaria-helminth infections. Mapping of malaria has undergone a renaissance following an increased recognition that malaria interventions such as IPTi and vector control approaches must be guided by effective cartography of malaria endemicity risk.94 In addition, the value of a geographical perspective to helminth epidemiology and control has long been recognized, and has been supported by the recent use of GIS and remote sensing.2, 3, 96 Geographical congruency of different parasite species can be based initially on climate-based disease risk maps, such as those presented here used to model plasmodium-STH co-distribution.6 Such maps, however, however, belie the geographical variation evident at the community level which is difficult to capture with existing risk models, and there is a requirement for more detailed empirical data collected through structured field surveys. For example, in light of recent evidence suggestive of a negative spatial association between *W. bancrofti* and *P. falciparum* in west Africa,97 the distribution of LF and malaria at local scales urgently needs to be better determined. Moreover, it remains unclear how patterns of co-distribution actually relate to co-infection, and how distributions of co-infection vary with environmental and socio-economic heterogeneities. Interpretation of future survey data would, in turn, be facilitated by geostatistical models which will help to identify significant spatial risk factors and predict patterns of co-endemicity and co-infection. To date, only one study has attempted to model the spatial occurrence of co-infection,98 and it showed that it was possible to predict spatial patterns of *S. mansoni* and hookworm. An improved understanding of spatial risk factors will allow the projection of co-endemicity on the basis of remotely sensed satellite data to allow for improved co-infection disease burden estimates. Newly refined endemicity maps will provide the basis for rational implementation of combined control by deriving more-accurate commodity and budget estimates for different intervention types and mixes within countries.

Third, because the mix of optimal interventions will depend of the level of parasite transmission, there is a need to determine the cost-effectiveness of different intervention combinations in a range of endemicity conditions. An anticipated benefit of combining malaria and helminth control in Africa would be the health gains that could result from reducing anemia. As indicated, possible options include the linkage of IPTp with deworming to tackle maternal anemia and the combined delivery of IPT and deworming through schools to improve hemoglobin levels. In addition to these immediate health impacts, they may also

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be benefits on, often neglected, non-health benefits including cognition and school performance.

Combining different interventions may yield what economists call economies of scope, thereby resulting in lower average costs.99 However, this may also cause diseconomies of scope (increasing average costs), whereby adding more treatments overloads capacity and the current intervention is delivered less efficiently.100 This aspect deserves critical attention as integrated programmes are rolled out. There are also a number of operational research questions that would require attention, including optimising delivery systems, identifying appropriate drug combinations, devising appropriate monitoring and evaluation. Finally, the safety of different IPT and anthelmintic drug combinations needs to firmly established before interventions can be rolled out.

CONCLUSIONS

Early hypotheses on malaria-helminth interactions arose from studies documenting the potent immune responses evoked by helminths and the Th1/Th2 hypothesis. More recent attention has focused on the potential impact of co-infection on hemoglobin levels and the relevance of an integrated approach to controlling childhood anemia. However, the epidemiological evidence base on co-infection is currently inadequate, and there is a need to adopt a credible, data-driven approach to resolve key scientific and programmatic questions. We have presented preliminary analysis of available data to investigate issues, but it is clear that further detailed study in a range of parasite transmission settings is warranted. We would argue that co-infection and its impact on anemia should be investigated in the same rigorous way that single parasite species has been investigated, thereby allowing the development of a realistic framework to prioritize resources and to anticipate potential intervention impact. Several opportunities for combining malaria control with anthelmintic treatment currently exist, and we would suggest that combined intervention would be particularly relevant for vulnerable populations who are at the highest risk for anemia such as children and pregnant women. However, relevant interventions should be tailored to the epidemiological conditions so that resources are optimally targeted.

Acknowledgments

We thank Lani Stephenson and Caroline Shulman for allowing us to re-analyse their data.

Financial support: SB is supported by a Wellcome Trust Advanced Training Fellowship (#073656). SB and PJH acknowledge support of the Albert B. Sabin Vaccine Institute's Human Hookworm Vaccine Initiative (HHVI) funded by the Bill and Melinda Gates Foundation. RP is supported by a Medical Research Council DTA-funded studentship. RWS is a Wellcome Trust Principal Research Fellow (#079080) and acknowledges the support of the Kenyan Medical Research Institute.

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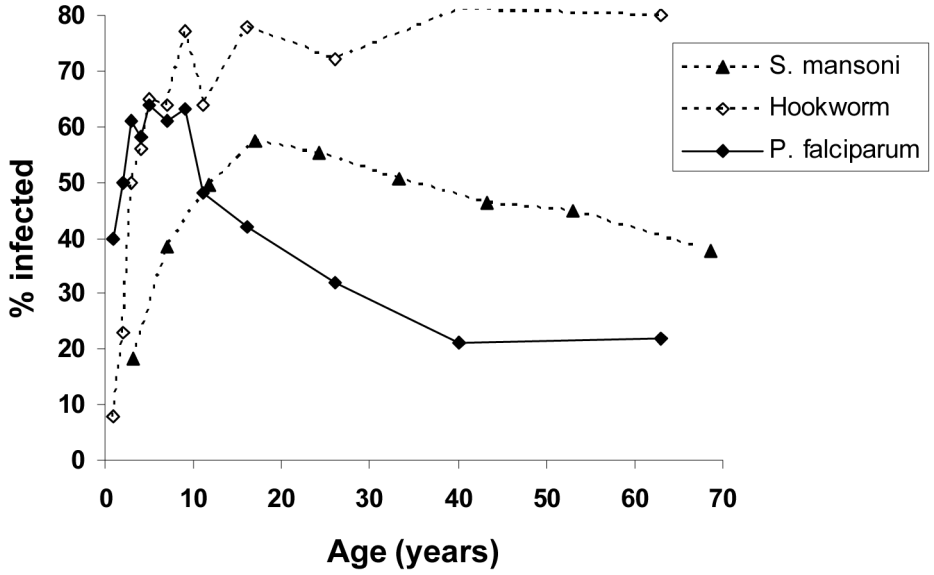

FIGURE 1.
Typical age profiles of prevalence *P. falciparum* infection, hookworm and *S. mansoni*. Data taken from Ashford et al. 103 and Kabatereine et al. 104

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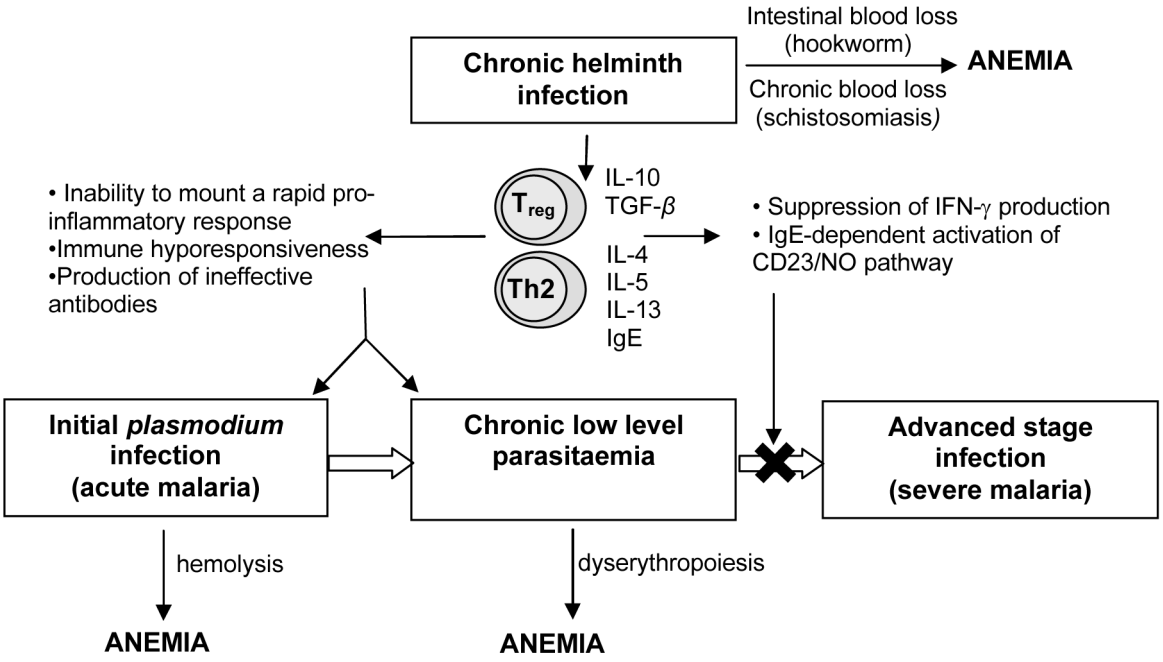

FIGURE 2.

Plasmodium-helminth co-infection: hypothesised mechanisms through which helminths may alter the risk of malarial infection and disease, and the mechanisms through which anemia arises. Chronic helminth infection induces a T-helper 2 (Th2) cytokine response, which may impose cross-regulatory effects on the development of an appropriate pro-inflammatory response to initial malaria infection,105-108 and skew anti-*plasmodium* antibody responses towards the production of non-cytophilic immunoglobulins ineffective against malaria (IgG4 and IgGM), instead of cytophilic ones necessary for immunity (IgG1 and IgG3).109, 110 However, induction of an anti-inflammatory immunosuppressive network may in fact prevent severe pathology in the later stages of malaria infection, with high levels of helminth-induced interleukin(IL)-10 111-114 acting to down-module the effects of interferon (IFN)-γ and tumor necrosis factor (TNF)-α, thus reducing malaria pathology.8 Alternatively sequestration of infected red blood cells may be prevented through IgE-mediated activation of the CD23/NO pathway.115 Adapted and expanded from Hartgers and Yazdanbakhsh.8

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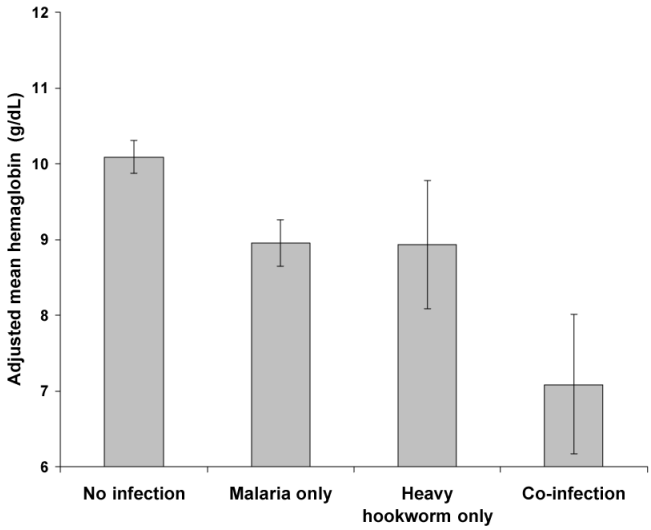
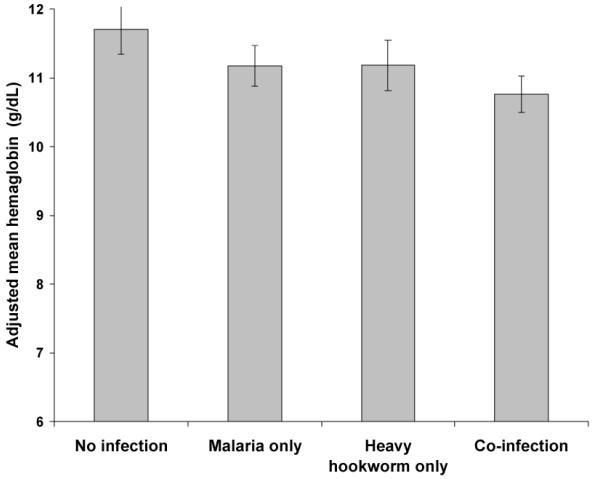
(a)



(b)



(c)

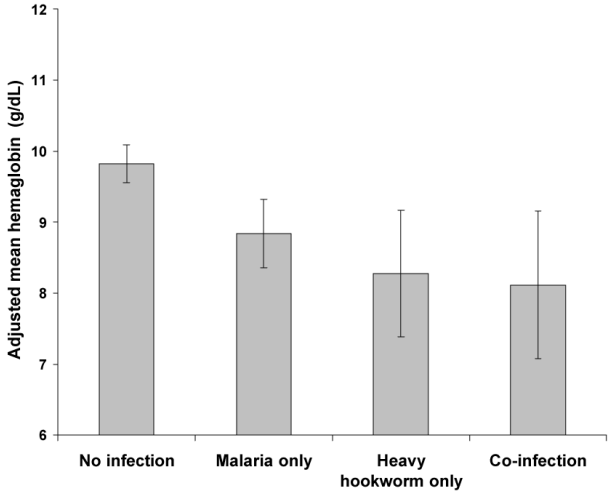


FIGURE 3.

The relationship between plasmodia-hookworm co-infection and mean hemoglobin concentration in Kenya based on re-analysis of published data. (a) Pre-school children: 460 children among whom 61.5% were uninfected; 30.9% infected with *P. falciparum* alone; 4.1% with heavy hookworm (eggs/gram feces (epg)>2000); and 3.5% with both, based on Brooker et al.116 (b) School-age children: 392 children among whom 19.1% were uninfected; 27.8% infected with *P. falciparum* alone; 17.9% with heavy hookworm (eggs/gram feces (epg)>2000); and 35.2% with both, based on Stephenson et al. (1985).48 (c) Pregnant women: 251 women among whom 68.5% were uninfected; 21.1% infected with *P. falciparum* alone; 6.0% with heavy hookworm (eggs/gram feces (epg)>2000); and 4.4% with both, based on Shulman et al. 117. Mean hemoglobin based on regression modelling adjusting for age and sex, and nutrition and socio-economic status (pre-school children) and gestation (pregnant women). Error bars indicates 95% confidence intervals.

Table 1

School-aged population (millions) at risk in 2005 of co-infection of *Plasmodium falciparum* and soil-transmitted helminth (STH) infection. Analysis extended from Ref 5.

STH[a] and *P. falciparum*[b] risk	African school-age population (millions) exposed to risk of co-infection
A. lumbricoides	
Stable endemic	17.87 (17.44-18.29)[c]
Acute seasonal	5.76 (5.59-5.92)
Marginal	1.61 (1.56-1.66)
T. trichuria	
Stable endemic	21.59 (21.21-21.97)
Acute seasonal	6.99 (6.85-7.14)
Marginal	1.75 (1.70-1.79)
Hookworm	
Stable endemic	32.05 (31.44-32.67)
Acute seasonal	9.55 (9.34-9.78)
Marginal	3.36 (3.18-3.52)

[a] Predicted prevalence of STH based on species-specific models of the relationships between observed prevalence of infection among school-aged children for 1172 sites across sub-Saharan Africa and satellite-derived environmental data (temperature and vegetation) and elevation data. All surveys were conducted using similar diagnostic techniques (direct smear, typically using the Kato-Katz method) and based on random samples of children in areas where no control measures have previously been undertaken. For further details, see Brooker et al.2

[b] Based on a climate-driven model of malaria suitability which has previously been used to classify populations exposed to risk of stable malaria and epidemic malaria (Craig et al., 1999). This model provides Fuzzy Climate Suitability (FCS) values, ranging from unsuitable [0] to completely suitable [1] for stable *P. falciparum* transmission. We adopted a modified classification of this risk criteria used in previous estimations of childhood populations at risk of different transmission conditions17, 18: zero risk [FCS = 0], marginal risk [FCS >0-<0.25], acute seasonal transmission [FCS >0.25-<0.75] and stable endemic transmission [FCS >0.75]. The FCS risk classes were additionally adjusted for the suppressive effects of urbanization on malaria transmission using the approach developed by Hay et al. 17

[c] Populations at risk based on projected 2005 school-age population estimates which were abstracted from the Gridded Population of the World version 3.0101 and country-specific medium variant population growth rates and proportions of the population aged 5-14 years from the United Nations Population Division – World Population Prospects database.102 The combined STH- and malaria-risk and population models were used to estimate the populations at risk of co-infection. To estimate the combined risk of STH and *P. falciparum*, independence between species was assumed. Ninety-five percent confidence intervals are based on those calculated for the predicted STH prevalence. For further details, see Brooker et al.6

Table 2

Potential malaria and helminth control strategies which could be combined. Expanded from Ref[19]

Population	Malaria	STH and schistosomiasis	Lymphatic filariasis	Onchocerciasis
Infants and pre-school children	IPTi/IPTc[a] ITNs	Regular treatment with ABZ & PQZ[b]	NR[c]	NR[c]
School-age children	IPT in schools[a] Health education to promote ITN use and prompt effective treatment	Regular treatment with ABZ & PQZ Health education on prevention Improved sanitation		
Pregnant women	IPTp ITNs	Regular treatment with ABZ & PQZ[d]		
Community-based control	ITNs Health education to promote ITN use and prompt effective treatment	Regular treatment with ABZ & PQZ Health education on prevention Improved sanitation	Annual CDT with ABZ plus IVM[e] or with ABZ plus DEC[f] Vector control where appropriate	CDT treatment with IVM Vector control where appropriate

IPTi = Intermittent Preventive Treatment in infants; IPTc = Intermittent Preventive Treatment in young children; IPTp = Intermittent Preventive Treatment in pregnancy; ITNs = Insecticide Treatment Nets; ABZ = Albendazole; PQZ = Praziquantel; CDT = Community-directed treatment; IVM = Ivermectin; DEC = Diethylcarbamazine.

[a] Not yet recommended by WHO and is the subject of ongoing evaluation

[b] To children aged one year and above

[c] Not recommended

[d] In second and third trimester of pregnancy

[e] In areas co-endemic with onchocerciasis

[f] In non-endemic onchocerciasis areas