

Pregnancy, Nutrition and Parasitic Diseases¹

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ABSTRACT In the developing world, young women, pregnant women, and their infants and children frequently experience a cycle where undernutrition (macronutrient and micronutrient) and repeated infection, including parasitic infections, lead to adverse consequences that can continue from one generation to the next. Among parasitic infections, malaria and intestinal helminths coexist widely with micronutrient deficiencies and contribute importantly to anemia and this cycle of retarded growth and development. In somewhat more limited or focal geographic settings, other parasitic diseases (e.g., schistosomiasis, filariasis) contribute similarly to this cycle. It is undoubtedly much better to enter a pregnancy free of infection and nutritionally replete than the various alternatives. Existing intervention strategies for micronutrient support and for the control of common parasitic infections before or during pregnancy, particularly malaria and intestinal helminths, should be followed. However, further research to identify barriers and priority approaches to achieving this goal remain very important in resource-poor settings where targeted public health efforts are required. *J. Nutr.* 133: 1661S–1667S, 2003.

KEY WORDS: • pregnancy • malaria • anemia • intestinal helminths • parasitic diseases

In the developing world, young women, pregnant women, and their infants and children frequently experience a cycle where undernutrition (macronutrient and micronutrient) and repeated infection lead to adverse consequences that can continue from one generation to the next. Infants born prematurely or with low birth weight (LBW)³ are at increased risk of early death but are also at risk of poor growth and development in childhood and adolescence. The poor growth resulting in underweight and stunting leaves reproductive-age women at risk in their early pregnancies of delivering premature or LBW infants (1). In addition, the micronutrient deficiencies, particularly iron and folate deficiencies (which contribute to anemia), leave the young women at risk of anemia leading to inadequate oxygen-carrying capacity and risk in pregnancy of delivering premature or LBW infants (1). This cycle (**Fig. 1**) is affected in each age group (infants, children, adolescents and reproductive-age or pregnant women) by prevalent parasitic infections. Of particular note, malaria and hookworm infections are widely prevalent in poor areas and both are recognized as contributing importantly to this cycle (3,4). Other parasitic infections may be less common or more geographically localized but also contribute to this cycle.

The effects of parasitic infections on nutrition, particularly nutritional status in pregnancy, and risks in the next generation are discussed here. Emphasis is given to malaria and intestinal helminths because of their wide distribution and direct effect on nutrition and during pregnancy. Options for combined intervention strategies are also discussed.

Preexisting conditions in young nonpregnant women of reproductive age

The health status of young women before pregnancy is a critical determinant of the risks that may ensue during pregnancy. Young women who experience one or more problems, including stunting, low weight, anemia through its multiple causes or chronic infection, will start a pregnancy at great disadvantage. Women who are underweight or stunted, those with anemia from one or more causes (e.g., iron deficiency, malaria, intestinal helminth infection) and those with certain infectious diseases (e.g., malaria) are at increased risk of delivering LBW infants (1,3,5,6). LBW and premature infants have a much increased risk of early child mortality (7–9) and impaired growth and cognitive development (10,11).

Parasitic infections, nutrition and pregnancy

Malaria. Malaria infection is endemic across the tropics and subtropics; affects people in more than 90 countries; causes 300–500 million infections each year; and is estimated to lead to approximately 1 million deaths each year, mostly in young children (12,13). Most infections and the most severe morbidity and mortality are caused by *Plasmodium falciparum*. The other three human malaria parasites (*P. vivax*, *P. malariae* and *P. ovale*) contribute to fewer infections and to more mod-

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³ Abbreviations used: IUGR, intrauterine growth retardation; LBW, low birth weight.

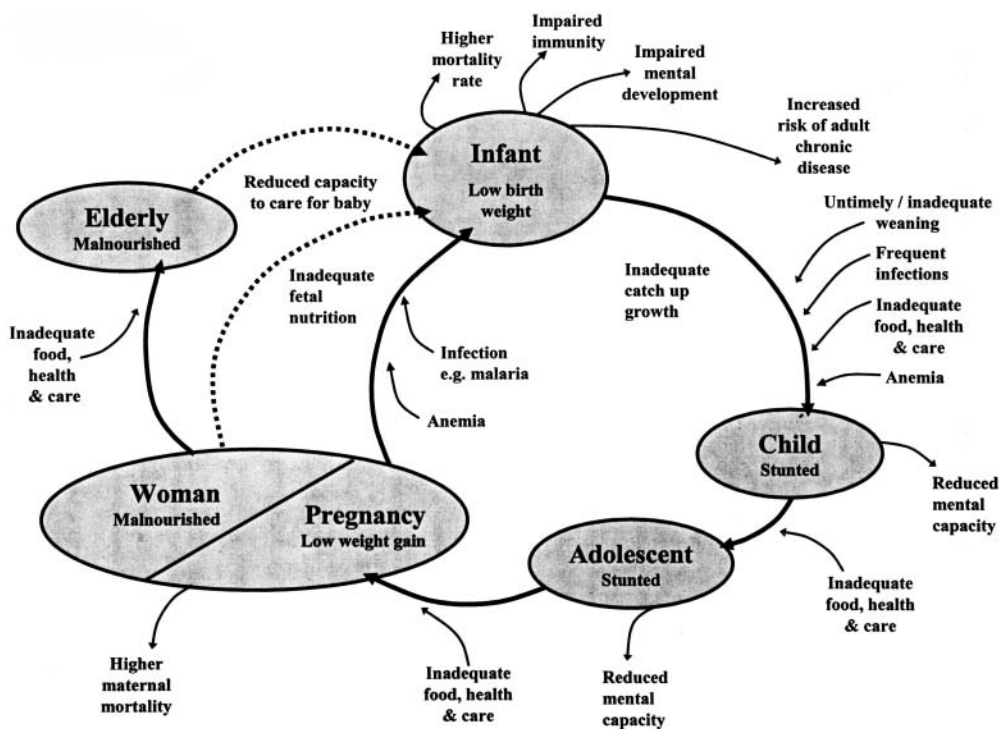


FIGURE 1 Cycle of adverse events throughout life associated with undernutrition and infectious diseases. Infections (e.g., malaria) increase nutrient requirements and contribute during pregnancy to anemia and low birth weight and during childhood to anemia and child stunting. Data from reference 2.

erate disease and relatively few deaths (14). Most *P. falciparum* infections and consequences are in sub-Saharan Africa, but Asia, Southeast Asia and the Americas are also sites of transmission for this parasite. Although a few reports of adverse consequences of *P. vivax* in pregnancy exist (15), *P. falciparum* is the only human malaria parasite that is more common in pregnant than in nonpregnant women and is the only human parasite with a clear and substantial adverse effect on pregnancy, nutrition during pregnancy and pregnancy outcome (3,16,17).

Erythrocytes infected with *P. falciparum* congregate in the maternal placental vascular space where the sinusoidal and low pressure blood flow, and possibly parasite adherence to endothelial cells (18), allow parasites to sequester and replicate. An active immune response involving antibody production, cytokine release and a cellular response (principally a basophilic monocytic macrophage response) is frequently observed in malaria-infected placentas (19). The infection and, possibly, aspects of the immune response contribute to poor pregnancy outcomes of prematurity and fetal intrauterine growth retardation (IUGR) (9,20). These adverse consequences appear to be mediated through several different pathways. The effect on prematurity is not entirely clear, but women with an active parasite infection and a fetus exposed to parasitized maternal erythrocytes (9) may develop an immunologic response that contributes to stimulus of early onset of labor. The effect of malaria on IUGR appears to be basic to the system of nutrient transport to the fetus. High-density or prolonged parasite infection in placental blood and the consequent cellular immune response may require substantial nutrients and thus leave less nutrient (glucose and oxygen) available for passage to the fetus. In addition, histopathologic studies of malaria-infected placentas demonstrate thickening of cytotrophoblastic membranes, which may alter nutrient transport to the fetus (19). Although the details of these biological processes are difficult to study except when the placenta is delivered, the overwhelming evi-

dence of many studies suggests a clear adverse effect of malaria on LBW and prematurity (3,21).

Malaria also clearly contributes to anemia throughout life and specifically during pregnancy. In a recent review of studies of *P. falciparum*-related anemia in pregnant women, Guyatt and Snow (22) suggest that approximately 400,000 pregnant women develop moderate or severe anemia (hemoglobin <80 g/L or hematocrit <0.25) each year in sub-Saharan Africa as a result of malaria infection. Studies have shown that maternal anemia contributes independently to LBW through IUGR (19,23,24) and to infant mortality (24). Although the specific biological processes are not clearly delineated, the contribution of moderate and severe anemia to poor oxygen transport to the developing fetus is a likely mode of action for anemia's adverse effect on fetal growth. In addition, malaria-associated anemia in the mother likely has important consequences on her outcome whereby already anemic women are at increased risk of severe consequences (e.g., hypotension, shock, death) even with a moderate ante- or postpartum hemorrhage.

Malaria in early childhood has long been thought to contribute to lasting undernutrition. Recently, in intervention studies with very malaria-specific interventions (e.g., insecticide-treated bed nets), malaria prevention was shown to substantially reduce the frequency of early stunting in children (25), suggesting that malaria contributes directly to stunting and that this is reversible in early childhood. This malaria effect on stunting then contributes further to the cycle noted above where poor nutrition in childhood (e.g., early and recurrent infection with *P. falciparum*) leads to short and small reproductive-age women who risk a poor pregnancy outcome.

With the development and rapid expansion of the HIV epidemic, particularly in sub-Saharan Africa, investigators have observed the worsening of malaria and its consequences in pregnancy. In malaria-endemic settings, women with HIV infection are at greater risk of having malaria, placental malaria infection and higher-density parasitemias with the infection;

both HIV and malaria contribute independently to maternal anemia and LBW infants (26–30). Although not as clearly documented, the effect of HIV on nutrition has been described for iron, folate, vitamin A and other deficiencies (31–33), and dual HIV and malaria (or other parasite) infection may have a substantial effect on nutrition.

Treatment of malaria during pregnancy is highly effective in clearing or reducing placental infection, anemia and LBW consequences (3). Because of the high frequency of *P. falciparum* infection in many African settings, a preemptive approach using intermittent preventive treatment at regularly scheduled antenatal clinic visits and providing insecticide-treated bed nets for each pregnant woman has been shown to be highly effective; this approach was adopted by the Roll Back Malaria partnership and established as policy in a number of countries (3,25,34). Studies have shown that additional supplementation of iron (35) and other micronutrients, possibly including vitamin A (36) and folate (37), should be coupled with antimalarial use for anemia and LBW prevention in pregnancy (36).

Intestinal nematodes. Intestinal worm infections are common worldwide but thrive in poor communities in the tropics where poor water supply and poor sanitation are common. The burden of infection is estimated to exceed 1000 million infected persons each for roundworm (*Ascaris lumbricoides*), hookworm (*Ancylostoma duodenale* and *Necator americanus*) and whipworm (*Trichuris trichiura*) (38,39). Although acute symptoms of infection are uncommon, numerous studies have shown a consistent association between intestinal nematode infection and diminished food intake and weight loss (40–42).

Of particular note, hookworm infection causes mechanical laceration and enzymatic damage to the mucosa of the small intestine leading to approximately 0.05 mL/d of blood loss per adult *Necator americanus* and approximately 0.25 mL/d per adult *Ancylostoma duodenale* (43). The hypochromic microcytic anemia follows chronic infection within 3–5 mo after exposure. These infections may predominate in young and school-age children but their consequences in chronic undernutrition and anemia in reproductive-age women are considerable. Data from the early 1990s suggest that 44 million of the developing world's 124 million pregnant women harbored hookworm infection (44). Although it has been difficult to measure and attribute the LBW and decreased child growth caused by hookworm, recent intervention trials using effective drugs against intestinal helminths showed significant improvements in child weight, weight for age and weight for height (45). The gastrointestinal blood loss, malabsorption and appetite inhibition (46) may further aggravate the iron, zinc and protein-energy deficiencies and the anemia of pregnancy. Intervention studies suggest that even relatively light hookworm infections may decrease fetal growth and weight gain in pregnancy (47).

The World Health Organization recommends four antihelminthic drugs for the control of intestinal nematodes including hookworm and a World Health Organization Informal Consultation suggested that the drugs albendazole, levamisole, mebendazole, pyrantel and praziquantel could be used in strategies designed to improve the health, development and nutritional status of girls and women and that single-dose, oral anthelmintic treatment can also be given to pregnant and lactating women (stressing that these drugs should not be used in the first trimester of pregnancy as a general precautionary measure) (48–50).

Other parasitic infections. The specific effect of other parasitic infections on nutritional factors affecting pregnancy and pregnancy outcomes is less well documented. The frequency and geographic distribution of some of these infections is

great (e.g., schistosomiasis, filariasis, giardiasis) but other infections are more localized or relatively less common in reproductive-age women. Information on many of the specific effects of acute parasite infections during pregnancy or with congenital infection has been reviewed elsewhere (51). Although it is easy to imagine that infection with any of these parasites is not good for the nutritional status of pregnant women, specific data for each of these parasitic diseases are limited. As a consequence—and not because of their importance or the importance of their control in the broader population—the priority placed on these diseases for specific pregnancy-focused intervention strategies is currently lower than the priority for malaria and intestinal helminths. Some of the common parasites are briefly discussed below in this context.

Schistosomiasis, principally caused by *S. haematobium*, *S. japonicum* and *S. mansoni*, is endemic in 74 countries and infects more than 200 million people worldwide (52). Child growth patterns and school performance are adversely affected by infection but are reversible with therapy. Women of reproductive age may experience genital tract infection with disease in the pelvis affecting the renal system and the genital tract including salpingitis and tubal obstruction with possible ectopic pregnancy. As a systemic disease that causes anemia, schistosomiasis may have consequences similar to those described for hookworm infection. Investigators have demonstrated this blood loss and anemia from *S. mansoni*, *S. japonicum* and *S. haematobium* (53,54). Some case reports of congenital infection exist and *S. haematobium* eggs have been recognized in placental blood (55), but other than the anemia noted above, there is little documentation of other widespread pregnancy-associated consequences of schistosomiasis. Because the treatment for schistosomiasis with praziquantel is relatively simple and considered safe at least in the second and third trimester of pregnancy, case management during pregnancy can be considered and would likely have important benefits in endemic settings (49,50).

Filariasis is endemic in more than 80 countries and an estimated 120 million people are infected (two-thirds of infected people are in India and sub-Saharan Africa) (56). This blood-borne parasite leads to local inflammation with lymph node involvement, including in the pelvis and possibly affecting reproductive organs; there is little evidence that it contributes to specific adverse nutritional outcomes (45).

African trypanosomiasis (sleeping sickness caused by *Trypanosoma gambiense* or *T. rhodesiense*) and American trypanosomiasis (Chagas disease caused by *T. cruzi*) affect substantial populations in their respective continents and can infect women during pregnancy and lead to congenital infection of the newborn. However, other than the general effect of systemic illness on limiting food intake and causing increased energy requirements for coping with the infection, there is no evidence for specific effects on maternal or fetal nutritional status.

Many other parasitic diseases may have acute systemic consequences in infected individuals, which may include pregnant women, but they have no broader documented contribution to nutritional deficiencies during pregnancy. Other reviews of these parasitic infections can be consulted for further information on case identification and management (51,54,57,58).

Micronutrient deficiencies and parasitic infections

The consequences of parasitic infections on human nutrition and the consequences of undernutrition on parasitic infections and their outcomes are clearly intertwined. Recent

reviews of micronutrient malnutrition and malarial anemia (59); malnutrition and parasitic helminth infections (4); and malnutrition, infection and immunity (60) suggest a strong link among protein-energy malnutrition, micronutrient deficiency, infection and bad outcomes. Some of the general knowledge regarding interactions among micronutrient deficiency, anemia and infections with parasites are summarized in **Table 1**. Although these interactions are not specific to pregnancy, the increased demands on micronutrients during pregnancy exacerbate the deficiency and its consequences.

Of particular note, in addition to their contribution to adverse pregnancy events and outcomes, micronutrient deficiencies may contribute to an increased risk of parasite infection or high-density infection. This increased risk has been suggested for iron (62,63), vitamin A (64) and zinc (63,65–68). In developing countries where poverty is the norm and micronutrient deficiency (including vitamin A and zinc deficiency) and parasite infections are common, there remains a relatively limited set of clear treatment and supplementation recommendations that focus on iron (69–72), folate (73–75), malaria (76) and intestinal helminths (48,49). Even for these clear recommendations, questions remain about optimal delivery strategies (69). Guidance for vitamin A and zinc supplementation in pregnancy exist but are somewhat more cautionary for vitamin A, with concern expressed on the need for supervised delivery to address possible overdosing during pregnancy (77,78). For zinc the recommendations are more focused on specific populations of women at particular risk of deficiency (79–81).

Intervention opportunities

Because the cycle of infection (Fig. 1) suggests that for many parasitic infections the effect may occur both during pregnancy and well before pregnancy, various opportunities to intervene may exist (82,83). In general, no one will declare that a drug for parasitic infections is safe during pregnancy. Thus, where possible, priority should be given to treating or preventing infections either before the first pregnancy or between

pregnancies. For conditions that are diagnosed during pregnancy or that must be treated or prevented during pregnancy (e.g., anemia, malaria, hookworm), the safety of the treatment must be balanced with the adverse consequences of the disease.

Currently, reproductive health programs encourage public health approaches during pregnancy for anemia, malaria and hookworm prevention and treatment because the substantial adverse consequences outweigh any risk associated with the prevention and treatment. These are meant to be part of routine antenatal care services provided particularly during the second and third trimester of pregnancy when the risk of the drugs for the mother and the developing fetus is thought to be small and the benefits have been clearly documented. In the developing world, relatively few women come for care before quickening, so this preventive management approach is well suited to begin with the first antenatal clinic visit. Because a relatively high proportion of pregnant women attend an antenatal clinic at least once (e.g., Demographic and Health Surveys show that in 30 sub-Saharan African countries with recent surveys, >70% of all pregnant women attended an antenatal clinic at least once in most (22 of 30) counties [61]; **Fig. 2**). This strategy of incorporating services within existing antenatal clinic systems is likely to reach a high proportion of at-risk women and could substantially interrupt the cycle of infection, undernutrition and adverse reproductive outcome.

When treatments are combined in a package of interventions, there is always a risk of interaction between treatments. For malaria and anemia, the question of possible adverse interactions between iron supplementation and malaria arises. Studies have suggested that iron supplementation that maintains adequate iron stores may lead to higher rates of malaria (84), raising concerns about iron supplementation in malaria-endemic setting. Other investigations demonstrated that iron supplementation is clearly associated with improved hematologic status and has not contributed to clinically relevant worsening of malaria (85–88). A consensus of experts strongly supports the role of both iron supplementation and malaria prevention in pregnancy (89); however, members of the group of experts continue to describe this controversy (84).

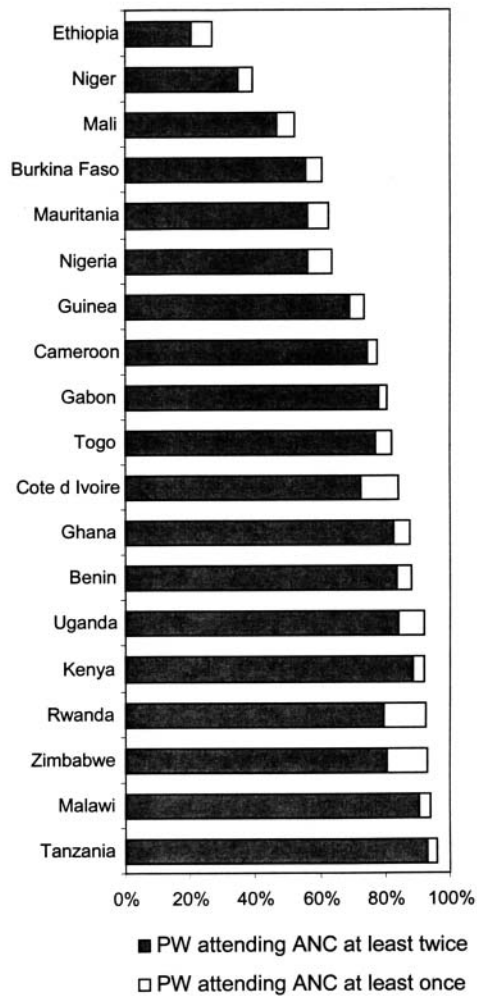
TABLE 1

Possible link among micronutrient deficiencies, parasitic disease (especially malaria) and anemia

Micronutrient deficiency	Possible role in anemia and impaired immune response to infection
Vitamin A	Increased susceptibility to malaria parasitemia, modulation of iron metabolism, deficit of retinol for synthesis of acute phase reactants
Vitamin C	Impaired T-lymphocyte response, delayed cutaneous hypersensitivity, impaired complement function, reduced phagocytic function
Vitamin E	Impaired T-lymphocyte response, altered B-cell function and impaired humoral response, delayed cutaneous hypersensitivity, impaired cytokine function or production, reduced phagocytic function; deficiency can contribute to oxidant damage to erythrocytes leading to hemolysis but deficiency can make the parasite more vulnerable to oxygen radicals generated with some antimalarial drugs
Riboflavin	Decreased iron absorption, increased erythrocyte fragility, depressed erythropoiesis; deficiency may protect against malaria by diminished parasite multiplication and growth but physiologic importance of this is unclear
Folate	Impaired erythropoiesis; deficiency may protect against malaria through impaired parasite metabolism but physiologic importance of this is unclear
Copper	Possible involvement in acute phase response to infection
Iron	Impaired erythropoiesis, decreased T-lymphocyte response, altered B-cell function and impaired humoral response, delayed cutaneous hypersensitivity, impaired cytokine function or production, reduced phagocytic function; deficiency and associated microcytosis may reduce malaria parasite multiplication but preventive supplements with iron have not shown this to be an important problem (61)
Selenium	Unknown
Zinc	Impaired immune function including decreased T-lymphocyte response, altered B-cell function and impaired humoral response, delayed cutaneous hypersensitivity, impaired cytokine function or production, reduced phagocytic function; can contribute to increased parasitemia

Data from references 59 and 60.

Proportion of pregnant women (PW) attending antenatal care in sub-Saharan African countries*



* source: Demographic and Health Surveys (MACRO-ORC, ref 61) and UNICEF Multiple Indicator Cluster Surveys conducted between 1995 – 2002.

FIGURE 2 The proportion of pregnant women attending antenatal clinic care at least once during their most recent pregnancy. Data from reference 61.

Approaches to the diagnosis and treatment of less common parasitic diseases presenting as acute infection during pregnancy are likely to be addressed case by case. Recommendations for the management of these acute infections can be found elsewhere (57,58,90). Unless the infection threatens the pregnancy, many of the treatments are best postponed to the postpartum period.

Because many of the infections and nutritional consequences are chronic, the intervention strategies must consider opportunities for diagnosis and management or preemptive prevention before pregnancy. This is particularly true for anemia and the intestinal helminths; many women enter a pregnancy with these as preexisting conditions. Opportunities to engage young, nonpregnant women for preventive health efforts will be important but are not a reality in many developing countries. An opportunity certainly exists for women attending school but because education is not universally available and the poorest women are least likely to attend school and most likely to be exposed to the diseases, strategies to reach the women at greatest risk must consider other community-based options (44).

Future research needs

Because intervention programs are always best applied from a sound scientific basis of understanding of the disease, its consequences, its points of attack and the ability to introduce the interventions into existing programs, public health professionals have ongoing needs for research in all of the parasitic infections noted above. A review of research needs on the interactions of certain parasitic diseases (malaria, schistosomiasis, amebiasis, giardiasis, ascariasis and hookworm) and nutrition in humans was discussed approximately 20 y ago (91). Although some work has been done to clarify some of the questions, other questions remain unanswered. Further information is needed today on macro- and micronutrients during pregnancy and on interactions between them and parasitic diseases. A clear example of the needs are seen in the editorial on anemia and pregnancy in sub-Saharan Africa (5), where the problem is enormous. Our understanding has evolved, yet we still do not have clarity on a strategy and effective delivery methods for a package of micronutrient supplement coupled with malaria prevention and other parasitic or bacterial disease treatment or prevention.

For malaria and intestinal helminths and their contributions to anemia, existing information on the adverse consequences of infection before and during pregnancy provides sufficient justification for active programs. However, few programs fully implement these proven strategies and further knowledge is required to

- identify the components that are needed to establish a full program effort;
- evaluate new and alternative antimalarial drugs;
- evaluate the combined benefit of a package of interventions addressing malaria (with intermittent preventive treatment and insecticide-treated bed nets), anemia (with iron and folate supplements) and intestinal helminths (with an anti-helminth drug); and
- identify when and where vitamin A and zinc supplements should be part of this package so that public health officials can provide clear, implementable recommendations addressing safety, efficacy and cost-effectiveness of these interventions.

For the other parasitic diseases, especially those with wide geographic distribution, additional studies are needed to

- determine the link between infection and poor nutritional and pregnancy outcomes and the public health extent of the problem;
- establish the appropriate public health interventions if these studies demonstrate that the disease extent and burden merit a public health approach; and
- evaluate and update case diagnosis and management options so that individuals can be well managed for their specific infection and disease.

Overall, as evidenced by the information reviewed here, relatively little information exists on 1) the specific interaction in pregnancy between parasitic diseases and deficiencies in general nutrition and micronutrients, or 2) the benefit and role for linked infection prevention/treatment and general nutrition/micronutrients supplementation. Because of the clear links among poverty, undernutrition and infection, a systematic evaluation is needed of both macronutrient and micronutrient deficiencies and the benefits of supplementation in combination with systematic treatment or prevention for the infectious diseases, especially the parasitic diseases mentioned. This systematic approach should focus on the at-risk population of pregnant women but should also consider these issues in young children, adolescent girls and women between pregnancies.

The approach should address both biological interactions (e.g., among micronutrients, malaria, other parasites, anemia and adverse outcomes) and programmatic interactions, where commonalities in service delivery opportunities might allow for joint delivery of interventions.

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