

**Expert  
Consultation  
on Anemia  
Determinants  
and Interventions**

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*and*

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## **Executive summary**

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A meeting of 16 experts in nutrition, medicine, pediatrics, epidemiology, parasitology, and health policy and programming was held 16–17 September 1997 in Ottawa to understand more completely anemia's complex etiology. The specific objectives of the meeting were

- to analyze evidence on the determinants of anemia including deficiencies of iron, folate, other micronutrients; malaria; intestinal parasites; and genetic factors;
- to determine the relative contribution of each to anemia in different regions and age groups;
- to identify efficacious and effective interventions;
- to identify gaps in knowledge; and
- to consider how the above interventions will influence and be integrated into policies and programs.

Following state-of-the-art presentations and discussion on each determinant, participants used a simple matrix to look at all of the determinants concurrently and with respect to age, sex, and population physiologic subgroup. The matrix, developed using the example of sub-Saharan Africa, was used to assess the relative importance of each determinant for each age group. As a result of the exercise, it was apparent that, for sub-Saharan Africa, the most important determinant of anemia at every stage of the life cycle, except pregnancy and infancy, was diet, particularly bioavailability of iron. In pregnant women, malaria was the main determinant of anemia in malarious areas for primigravidae, and both inadequate iron intake and low bioavailability were the main determinants in multigravidae. Malaria and diet were the main determinants in infants in the first year of life in malarious areas. The exercise revealed that causality is a complex matrix that is locality specific. Participants identified gaps in knowledge and recognized the need for simple epidemiologic methods to assess the causes of anemia.

## **Introduction**

### **Opening remarks**

M.G. Venkatesh Mannar, Executive Director of the Micronutrient Initiative (MI), thanked participants for sharing their experiences and insights toward developing integrated strategies for controlling anemia. He noted that the control of iron-deficiency anemia continued to lag behind the progress made in reducing iodine and clinical and subclinical vitamin A deficiencies. He stated that the meeting presented an opportunity to develop a clear understanding of both the determinants of anemia and the type of interventions that are efficacious and effective, thus facilitating appropriate policy development and the mobilization of support for anemia alleviation programs.

The meeting stemmed from a request by Judith McGuire of the World Bank for a cross-disciplinary exercise. Anemia's complex etiology has not been fully elucidated over the years, and Dr McGuire felt there was a particular need to deal with the issue at this time, given the current emphasis on iron-deficiency control and renewed interest in both malaria and helminth control.

Desirable meeting outputs were

- to develop a consensus on etiology,
- to identify what remains unresolved, and
- to identify potential outcomes of certain types of interventions under different contexts.

It was agreed that a discussion of programs would be postponed until the basic underlying principles of causation had been elucidated. Finally, Dr McGuire suggested that consideration be given to how this consensus could be disseminated to the larger public health and nutrition field, particularly policy makers and program managers.

### **Structure of the report**

This report, which incorporates references to presentations and discussion points of the participants, is a record of the meeting and is intended to be used by researchers concerned with anemia and as a reference for program managers. It follows the general format of the meeting (Appendix 1): short state-of-the-art reports, given by designated experts, are followed by general discussion of all participants. The report provides a synthesis of the presentations and discussions which reflect the actual proceedings.

### **Definition of the problem**

Anemia is a condition of low circulating hemoglobin with serious and even life-threatening consequences which have been reviewed extensively elsewhere (Gillespie 1998). Anemia is actually a statistical construct: it is defined, with respect to an individual, as a state in which the hemoglobin concentration has fallen below a threshold lying at two standard deviations below the median for a healthy population of the same age, sex, and stage of pregnancy

(WHO/UNICEF/UNU 1997), as shown in Table 1. Since hemoglobin concentrations are also influenced by race and elevation above sea level, adjustments to the reference figures may be required.

**Table 1: Hemoglobin (Hb) and hematocrit (Hct) levels below which anemia is judged to be present.<sup>a</sup>**

Group/age/physiologic status	Critical level	
	Hemoglobin (g/dL)	Hematocrit (%)
Children		
6 months to 5 years	11.0	33
5-11 years	11.5	34
12-13 years	12.0	36
Men	13.0	39
Women		
Nonpregnant	12.0	36
Pregnant women	11.0	33
Severe anemia	7.0	–
Very severe (life threatening)	4.0	–

<sup>a</sup> Source: WHO/UNICEF/UNU (1997), adapted from WHO (1968).

In relation to iron status and anemia, there are two main stages in the reduction of body iron before the development of anemia:

- 1) **iron depletion** which is a decrease in iron stores, and
- 2) **iron deficient erythropoiesis** which develops when storage iron is depleted and iron absorption is insufficient to counteract the amount lost from the body through the feces, desquamated mucosal and skin cells, and menstrual blood loss among women. At this time, hemoglobin synthesis starts to become impaired and hemoglobin concentrations fall. If anemia ensues, the reduction in hemoglobin production is severe enough to lead to distortion of red cells, with microcytosis and hypochromia.

## Objectives of the meeting

The objectives of the meeting were as follows:

- to analyze evidence on the etiology of anemia (including deficiencies of iron, folate, other micronutrients; malaria; hookworm; schistosomiasis; etc.) with a view to determining the relative contributions of each to anemia in different regions and different age groups;
- to identify efficacious and effective interventions;
- to identify gaps in knowledge; and
- to consider how the interventions will influence and be integrated into policies and programs.

The outcome of concern was not specifically iron-deficiency anemia, but anemia due to all causes. Although it is not possible to define a hemoglobin cut-off with respect to functional

impairment, it is nevertheless well understood that anemia has more serious consequences than nonanemic iron deficiency and should thus be given priority attention.

## **I: ANEMIA DETERMINANTS AND INTERVENTIONS**

The etiology of anemia is one of multiple and interacting causes. Common causes of anemia in childhood in tropical Africa, for example, include malaria; nutritional deficiencies of iron, folate, protein, and possibly other micronutrients (such as vitamin A and riboflavin); pyogenic infections; and sickle cell disease (Fleming and Werblinska 1982). Chronic disorders secondary to AIDS and tuberculosis are now increasingly implicated.

In this section, the associations between the main types of determinant— dietary factors, malaria, intestinal parasites, HIV, and various hemoglobinopathies — and anemia are described.

### **Diet**

Anemia is usually related, at least in part, to iron deficiency. This is particularly true in Asia and the Americas where the prevalence of iron deficiency generally significantly exceeds that of anemia. In sub-Saharan Africa, particularly tropical Africa, this may not be the case and other causes of anemia such as malaria and folate deficiency may be more prevalent, as seen, for example, in northern Nigeria (Fleming 1981).

A simple approach to identifying relevant issues regarding the role of diet, with respect to other factors, in determining iron status was introduced by way of the following construct (Fig. 1).

The iron status of an individual is viewed here as a black box, being determined by the way in which a combination of “in” and “out” factors relate to that person’s particular requirement for absorbed iron. The latter is related to various factors such as age, gender, physiologic status, and preexisting iron stores. “In” factors include the form of dietary iron (heme or nonheme) and the concentration of various dietary constituents that either inhibit or enhance the absorption of dietary iron consumed (MacPhail and Bothwell 1992). Fortificant iron and iron supplements, where they exist, are other “in” factors.

“Out” factors on the other hand essentially refer to losses of body iron through blood loss which may be pathologic (e.g., intestinal helminth infection) or physiologic (e.g., menstruation, pregnancy, and blood loss during delivery).

In subsequent discussion it was pointed out that certain other factors and conditions would need to be factored in to make such a construct comprehensive— for example, the presence of the two genes (a recessive trait) for hereditary hemochromatosis that predisposes to iron overload. The malaria parasite also may have a profound impact on anemia, despite not readily fitting into this

“In” factors	“Black box”	“Out” factors
Dietary iron (heme or nonheme)	Determinants of need for absorbed iron	Physiologic factors
Inhibitors	Age <sup>a</sup>	<ul style="list-style-type: none"> <li>• basal losses</li> <li>• menstruation</li> <li>• child birth</li> </ul>
<ul style="list-style-type: none"> <li>• tannins</li> <li>• phytates</li> <li>• calcium</li> <li>• etc.</li> </ul>	Birth weight	Pathological blood losses
Enhancers	Growth demand	<ul style="list-style-type: none"> <li>• intestinal helminths</li> <li>• allergies<sup>b</sup></li> <li>• gut diseases</li> </ul>
<ul style="list-style-type: none"> <li>• ascorbic acid</li> <li>• etc.</li> </ul>	Pregnancy demand	
Fortificant iron	Existing iron stores	
Iron supplements		

<sup>a</sup> Gestational age is particularly important as preterm babies will have a particularly high requirement for iron.

<sup>b</sup> Immunologic response to allergens, in severe cases can lead to inflammation and ultimately enteropathy with resulting gastrointestinal blood loss.

**Fig. 1:** Important determinants of iron status.

construct (see “Malaria”). Unlike intestinal parasites, the malaria parasite does not cause actual blood-iron loss, but it affects how iron is used within the body.

Nevertheless, the construct is a useful tool for estimating the anemia risk status of certain population groups where prevalence data are not available. The risk status may be assessed on the basis of the presence, configuration, and intensity of the various factors described above.

The importance of iron bioavailability may be illustrated by comparing the habitual dietary iron intakes of various African populations with the current recommendations for dietary iron consumption of Canadians, for example, of different age, sex, and physiologic status. The latter range from 7 mg/day iron for infants to 13 mg/day among adolescent and adult females, rising to 23 mg/day for pregnant women in the third trimester. These recommendations are based on the assumption of an absorption of about 12% from a mixed diet. In many African countries in which millet, sorghum, or maize is the staple, a large amount of dietary iron may be derived from the staple (FAO/WHO 1988). Although individuals may thus consume at least a quantity of iron meeting recommended iron intakes, the actual percentage of iron absorbed may be very low — perhaps as low as 1–2%. Thus, bioavailability, not intake, is usually the limiting dietary factor.

Nutrient interactions are also important considerations with respect to iron absorption and use. Folate and vitamin B<sub>12</sub>, for example, modify iron use through their role in nucleic acid synthesis and red blood cell production (Velez et al. 1966). Riboflavin (Powers et al. 1993) and vitamin A (p. 5) may also affect iron use.

**Folate** deficiency, which occurs when absorbed folate does not meet requirements over time, may lead to anemia (Fleming and Werblinska 1982), increased susceptibility to infections (Brabin 1982), low birth weight (Scholl et al. 1996), neural tube defects (Rosenberg 1992), delayed growth in early childhood and adolescence (Harrison et al. 1985), delayed sexual development (Watson-Williams 1962), and an increased risk of coronary heart disease (Morrison et al. 1996). Folic acid is present in all foods of plant and animal origin, particularly liver, leafy vegetables, fruit, pulses, and yeast. In a mixed diet, absorption may be around 70%.

An individual may become folate depleted as a consequence of a folate-deficient diet, often seasonal, or from malabsorption following systemic infections or tropical sprue. Pregnancy and lactation exert a particularly high demand for folate, and demand may have pathological consequences as a result of malarial hemolysis or hemoglobinopathies.

Tissue folate stores may be depleted in up to one-third of pregnant women worldwide (FAO/WHO 1970) and prevalence may be particularly high in Africa and Asia (Fleming 1989; Baker 1981).

Folate deficiency has been described as a frequent complication of protein-energy malnutrition in both West and southern Africa (Osifo et al. 1974; Margo et al. 1978; Nkrumah et al. 1988) and as contributing to anemia (Fleming and Werblinska 1982; Van der Westhuyzen et al. 1986). High demands for folate in hemolytic anemia lead to megaloblastic anemia complicating the course of, for example, sickle cell disease (Serjeant 1985).

In a study carried out in the early 1960s, a distinct seasonal pattern of anemia among pregnant women in Ibadan, Nigeria, was attributed to seasonal folate deficiency before harvesting the new yam crop (Fleming 1970).

**Vitamin B<sub>12</sub>** is present in animal foods, but not plants (unless contaminated with bacteria), and is stored in the liver for long periods. Depletion of body vitamin B<sub>12</sub> stores takes years, and vitamin B<sub>12</sub> deficiency resulting from nutritional inadequacy is rare.

**Vitamin A** is involved in mobilizing stored iron, and poor vitamin A status has been reported to be associated with altered iron metabolism and iron-deficiency anemia (Mejia and Arroyave 1982; Suharno et al. 1993). Sommer and West (1996) have summarized studies in which vitamin A supplementation was found to produce a hemoglobin response, mostly on the order of about 1 g/dL. In a recent randomized controlled trial in anemic preschool children in Ethiopia, iron or vitamin A supplemented children showed an increase in hemoglobin (1.9 and 1.2 g/dL, for iron and vitamin A supplementation, respectively). However, the largest increase in hemoglobin (2.2 g/dL) occurred in children receiving both vitamin A and iron (Abdulaziz 1997). Also recently in a recent randomized placebo-controlled trial in Nepal, weekly supplementation with 23 000 IU vitamin A as retinol or beta-carotene resulted in a 45% reduction in anemia (defined as low maternal hemoglobin, <10 g/dL) among women who did not have hookworm infection (Stoltzfus et al. 1997). However, dietary sources of vitamin A such as some green leafy

vegetables, contain large amounts of tannins which inhibit iron absorption.

**Seasonality** is also an important issue with respect to anemia prevalence. A twofold increase in anemia prevalence was seen in school children in Mali, from 30% in April to 58% in October (Diallo 1997). During the same sampling periods, malaria prevalence also doubled and mean malaria parasite density quadrupled. In addition to seasonality in malaria prevalence, changes in dietary intake of iron or other nutrients such as vitamin A during the year may partially account for seasonal trends in anemia.

In general, assuming etiology is known, currently accepted daily iron supplementation interventions aimed at increasing the amounts of absorbed iron are known to be efficacious. However, the efficacy of dietary modifications in improving bioavailability, as well as the efficacy of alternative supplementation regimes, is still under investigation (Gibson 1997; Beaton and McCabe, Cross-project analysis of intermittent iron supplementation, personal communication<sup>1</sup>).

## **Malaria**

Several established mechanisms have been implicated in the etiology of malaria anemia including:

- acute and chronic hemolysis,
- secondary folate deficiency, and
- dyserythropoiesis.

Because other factors frequently contribute to anemia risk in many tropical countries, including iron deficiency, malnutrition, and genetic defects, it is difficult to estimate the percentage of anemia in a particular population that can be attributed to malaria (Fleming and Werblinska 1982). Anemia undoubtedly is a major health problem in children and pregnant women in malarious areas of tropical Africa as hospital statistics indicate that either malaria or anemia or both constitute the largest out-patient and admission criteria for many centres. In view of the magnitude of the problem there is an urgent need to address the following question: How much anemia does malaria cause in young children and pregnant women?

The following three approaches have been used to answer this question:

- 1) Estimation of risk ratio and population attributable risk in individuals with and without the presence of malaria parasites in their blood.
- 2) Estimation of the hematologic response to antimalarial therapy in subjects with clinical malaria or anemia associated with malaria parasitemia.
- 3) Estimation of the prophylactic efficacy of antimalarials in reducing anemia risk in cohort studies.

Each assesses the problem from a different perspective, and allowance should be made for both

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the level of acquired malarial immunity in the individuals studied and whether acute or chronic parasitemia is prevented or treated. In highly malarious areas estimates of hemoglobin (or packed cell volume) improvements with treatment of *Plasmodium falciparum* malaria would indicate that in infants and pregnant women (especially primigravidae) an average improvement of at least 1 g/dL would be expected (Verhoeff et al. 1997). For more anemic individuals this improvement is greater, reaching estimates of 3 g/dL in some studies (Bloland et al. 1993). Improvements will be greatest in those experiencing higher parasite densities at the time of infection (i.e., in younger infants and women in their first pregnancies).

Malaria is thought to be the primary cause of severe anemia (Hb < 7 g/dL) in at least 50% of subjects living in malaria-endemic areas. A recent study in Tanzania has confirmed the role of malaria as the largest contributor to the etiology of severe anemia in infants in highly endemic areas, accounting for about 60% of all cases, compared with iron deficiency, which accounted for about 30% of severe anemia episodes (Menendez et al. 1997).

Coexisting iron deficiency will exacerbate anemia (van Henshroek et al. 1995), but does not appear to limit the hematologic response to antimalarials. Hematologic response has even been proposed as a criteria for choice of first-line antimalarial therapy in areas where drug-resistant *P. falciparum* occurs.

The appropriateness of routine therapeutic iron supplementation in infants and children living in malaria-endemic areas has been questioned following conflicting evidence regarding the effects of iron deficiency/sufficiency on the severity of infectious diseases. Several reports (see box) have raised the possibility of increased susceptibility to malaria in individuals receiving iron, whereas others have found no such association. These apparent discrepancies may be explained by differences in dose, duration, route of administration and degree of malarial immunity in the study individuals as well as differences in the design and follow-up of the study cohorts.

#### **Iron supplementation and malaria risk—historical context**

Iron deficiency does not protect against malaria (Snow et al. 1991). However, parenteral iron is reported to increase the risk of respiratory infections and the prevalence and effects of malaria in infants (Oppenheimer et al. 1986, Smith et al. 1989). Standard oral iron supplements given to infants in the Gambia have been found to be followed by more frequent fever associated with high-density malaria parasitemia during iron supplementation (Smith et al. 1989), although these observations were not confirmed in infants in Togo (Chippaux et al. 1991), older children in the Gambia (Bates et al. 1987) and Papua New Guinea (Harvey et al. 1989), or in pregnant women in the Gambia (Menendez et al. 1994). Following treatment of malaria in Gambian children, iron supplementation was not associated with increased prevalence of malaria during supplementation, but with a better hematological response (van Henshroek et al. 1995).

In addition to the above studies, further interesting results have emerged from recent studies carried out in Tanzania and Ethiopia. A randomized, double-blind placebo-controlled trial of iron supplementation and malaria chemoprophylaxis in infants was designed and carried out in a rural

area of intense and perennial malaria transmission in Southern Tanzania (Menendez et al. 1997).

The study showed the following:

- groups that received iron supplementation had a lower frequency of severe anemia than those that did not receive iron;
- iron supplementation had no effect on the frequency of malaria; and
- groups that received malaria prophylaxis had lower frequencies of both severe anemia and malaria than the groups that did not receive prophylaxis.

It was concluded that malaria chemoprophylaxis during the first year of life is efficacious in preventing malaria and anemia, but apparently impaired the development of naturally acquired immunity. There was, however, no evidence of an increase in the severity of the disease in children previously chemosuppressed. The rates of all-cause and malaria-specific hospital admissions during the second year of follow-up, 1 year following the interventions, were similar in all treatment groups (and significantly lower in the chemosuppressed groups during the first year of life). Although the cohorts continue to be followed, the absolute risks of malaria and severe anemia by 18 months of age are lower in the children who received chemoprophylaxis than in those who did not. In conclusion, these findings argue against withholding effective malaria-control methods from anybody at risk of malaria, even if this treatment leads to a delay in the acquisition of immunity.

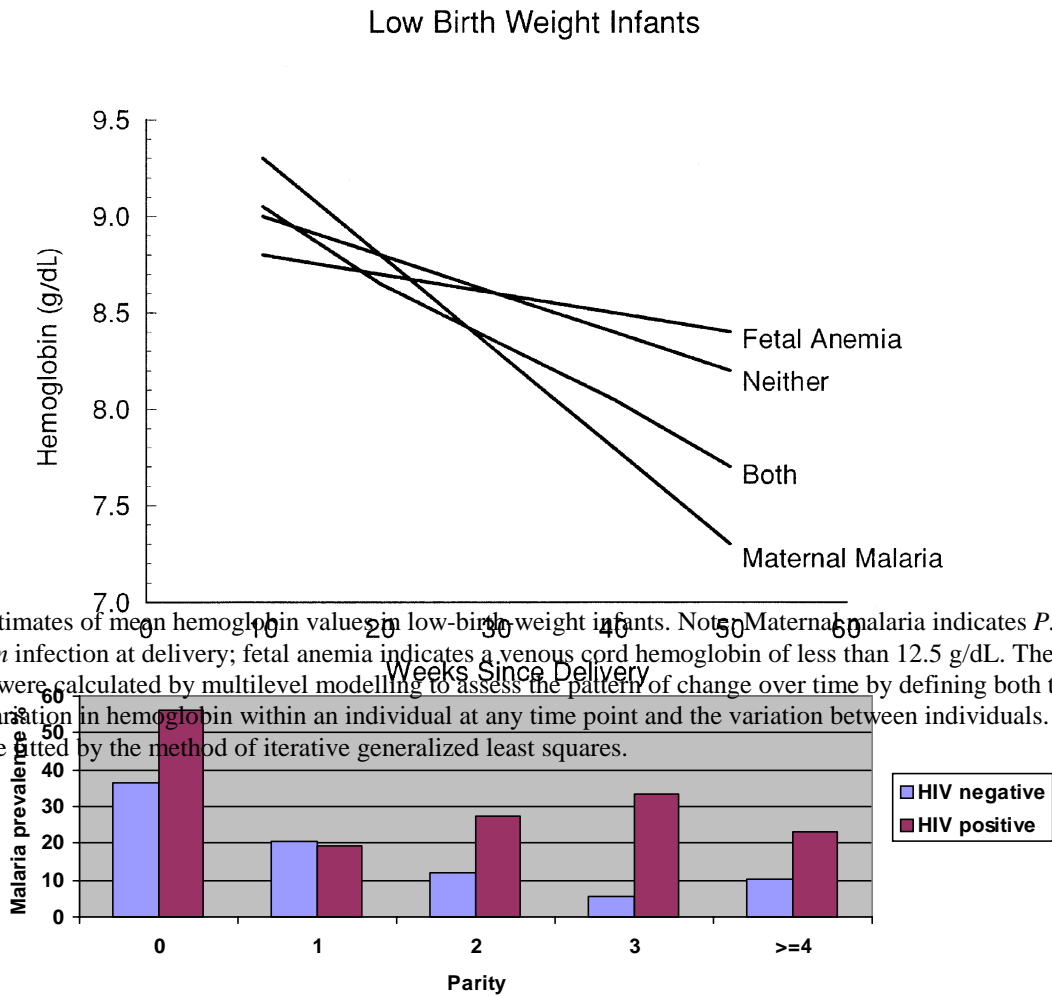
With respect to the potential of iron to increase the susceptibility to malaria, these findings strongly suggest that oral iron supplementation, at doses and durations adequate to replenish stores, does not increase susceptibility to malaria in infants during and 1 year after supplementation, but lowers by a third the rate of severe anemia. Supplementation through the mother was satisfactory, and further research and development of improved formulations and delivery mechanisms, with the aim of improving cost effectiveness, are now required. This study supports the large-scale provision of low-dose oral iron for the prevention of iron-deficiency anemia in infants, including those living in malaria-endemic areas.

In Ethiopia, results from two randomized double-blind, placebo-controlled field trials from the northwest of the country where malaria and iron-deficiency anemia coexist, have shown that supplementation with low-dose oral iron may increase the clinical risk of malaria in children (Hailemichael 1997; Adam 1997).

In one study, among children aged 5 to 14 years with mild to moderate anemia, although there was no increased malarial risk during the 3-month supplementation period, over the 24-week period following supplementation, 20.2 % of the 223 children receiving iron supplements had at least one clinical malaria attack compared with 14.0% among 222 children in the placebo group (Hailemichael 1997). In the second Ethiopian study (Adam 1997), 63% of anemic women receiving iron supplements experienced fever episodes during the 12 weeks of the trial compared with 55.3% among women receiving placebo. Similarly, 68.9% of anemic children between 6 and 84 months who received iron supplements were reported to have febrile episodes compared

with 58.9% of the children in the placebo group. This latter study reflects an increase 10% in excess of the risk of general morbidity due to malaria (increases in the number and duration of febrile episodes, clinical malaria attacks, parasitemia, and splenomegaly) in women of childbearing age and in children between 6 months and 7 years of age during 3 months of iron supplementation.

In both Ethiopian studies, however, there were highly significant improvements in hemoglobin concentration for the iron-supplemented groups. These studies concluded that, in areas where iron deficiency and malaria coexist, the benefit of iron supplementation outweighs the potential increased risk of malaria, and that integrated iron deficiency and malaria control strategies are essential in such situations.



**Fig. 3:** Prevalence of *P. falciparum* malaria by parity group in HIV-infected and noninfected pregnant women. Note: The data in Figs. 2 and 3 above represent preliminary information from a pregnant woman – infant cohort study in the Shire Valley of Malawi. The clinical field investigator for the study was Dr Francine Verhoeff, and the work was carried out under the auspices of the Department of Paediatrics, Medical College, Blantyre (Professor Robin Broadhead) (Verhoeff et al. 1996). This research was supported by the European Union Programme for Scientific and Technological Cooperation with Developing Countries.

The severity of malarial anemia relates to several factors that help to define specific at-risk groups. In children the main associated factors are age (which relates to parasite density) and hemoglobin or red cell genotype. Low-birth-weight babies (<2500 g) are at greatest risk of developing anemia during infancy, and studies from Malawi have shown this risk is further increased if the infant was born to mothers with malaria at delivery (see Fig. 2). In pregnant women, low parity, early gestational age, and human immunodeficiency virus (HIV) infection are associated with a higher prevalence of *P. falciparum* malaria. The impact of the latter has to be further evaluated but it would appear that HIV seropositivity is associated with higher prevalence of malaria in women of all parities, indicating that malaria-specific immunity acquired during earlier pregnancies is impaired, as shown in Fig. 3 (Brabin B, personal communication<sup>2</sup>).

Key aspects of this problem which require further evaluation relate to:

- Establishing the conditions under which iron supplementation in population groups at risk of anemia may increase susceptibility to malaria.
- Establishing more clearly the relationship between pregnancy anemia associated with malaria and infant anemia.
- Elucidating the causes of fetal anemia (i.e., low venous blood hemoglobin in the cord blood at delivery).
- Determining the magnitude of anemia risk in adolescent girls who are at risk of both iron deficiency, and malaria in their first pregnancy. Inappropriate antenatal care practices (i.e., quality of care such as antimalarial drug use in pregnancy) have been related to an especially high risk of low birth weight in this group (Verhoeff et al. 1998), as has the growth status of pregnant adolescents.
- Determining whether to screen or not screen for iron interventions based on infant birth weight and maternal malaria at delivery (Redd et al. 1994).
- Determining the cost-effectiveness of different integrated combinations of iron supplementation programmes with malaria control programs.
- Establishing the severity of folate deficiency anemia in children in malarious and non-malarious areas.

## Intestinal parasites

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Intestinal helminths affect over one quarter of the world's population at any one time (Table 2). Hookworms and schistosomes (*Schistosoma* spp.) are intestinal helminths which can contribute to anemia etiology where prevalent. *Trichuris trichiura* (whipworm) infection, particularly the *Trichuris* dysentery syndrome is associated with severe anemia and may affect 4% of some populations (Cooper and Bundy 1989). Light infections with whipworm are not associated with anemia. *Ascaris lumbricoides* has a small but significant inverse association with hemoglobin (Curtale et al. 1993; Stoltzfus et al. 1997). Hookworms (*Necator americanus* and *Ancylostoma duodenale*) which infect approximately 20% of the world's population, have the most significant effect (Stephenson 1987). Table 2 gives the regional breakdown of the estimated number of intestinal helminth infections.

Hookworms cause intestinal blood loss by feeding on blood through the intestinal mucosa. The relationship between hookworm burden and anemia is markedly nonlinear with heavy burdens having a disproportionate effect (Layrisse and Roche 1964; Lwambo et al. 1992; Stephenson et al. 1985a). Chronic fecal blood loss due to hookworm infection is a significant contributor to anemia (particularly moderate and severe anemia) among certain populations (Roche and Layrisse 1966; Srinivasan et al. 1987; Stoltzfus et al. 1997).

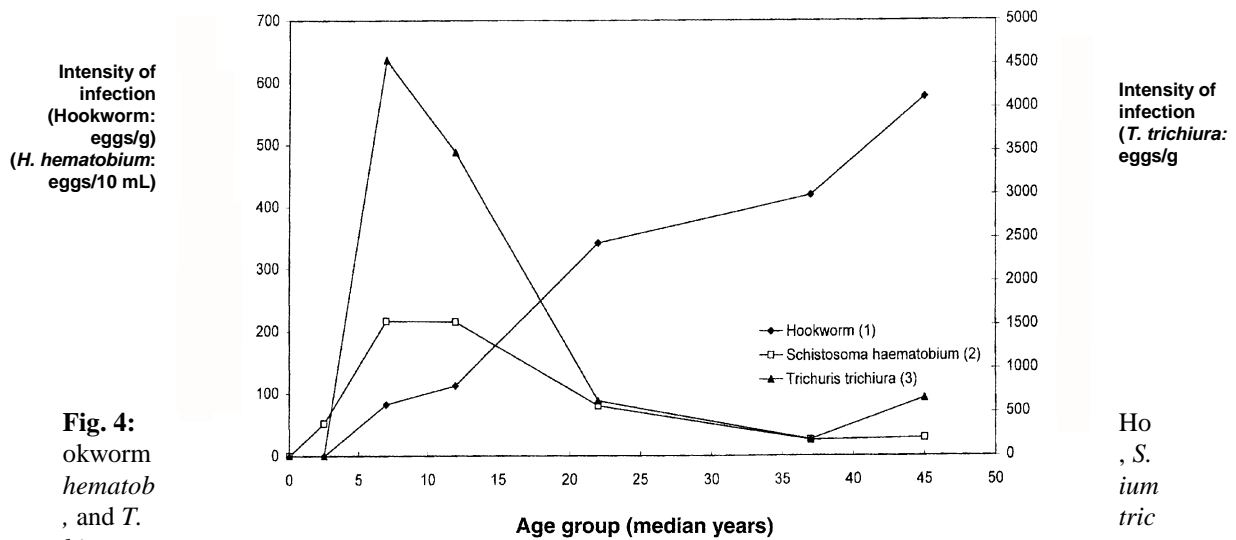
**Table 2: Estimates of number of selected helminth infections in the world (millions).<sup>ab</sup>**

Helminth	Region						Total
	SSA	LAC	MEC	IND	CHN	OAI	
<i>A. lumbricoides</i>	105	171	96	188	410	303	1273
Hookworms							
All	138	130	95	306	367	242	1277
Pregnant women	7.5	4.1	3.1	10.9	8.6	10	44.3
<i>T. trichiura</i>	88	147	64	134	220	249	902
<i>S. hematobium</i>	70	0	30	0	0	0	100
<i>S. intercalatum</i>	12	0	0	0	0	0	12
<i>S. japonicum</i>	0	0	0	0	10	85	95
<i>S. mansoni</i>	35	14	20	0	0	0	69
<i>S. makongi</i>	0	0	0	0	0	0.6	0.6

<sup>a</sup> Sources: Bundy et al. 1995; Bundy et al. 1997; Michael et al. 1997.

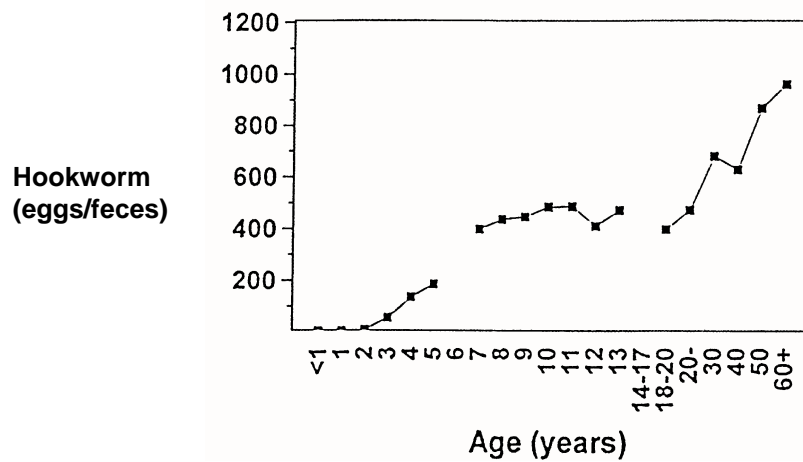
<sup>b</sup> Legend: SSA, sub-Saharan Africa; LAC, Latin America and Caribbean; MEC, Middle Eastern Crescent; IND, India; CHN, China; OAI, other Asian countries and islands.

Prevalence of hookworm infection increases with age and prevalence is higher among adults than children (Fig. 4). In highly endemic areas such as Zanzibar, Tanzania, the prevalence rises to a plateau at about 8 years, whereas the intensity (egg count in feces) continues to rise throughout life (Fig. 5). However, a convex hookworm–age profile has also been reported



**Fig. 4:** Intensity of infection (Hookworm: eggs/g) (*H. hematobium*: eggs/10 mL) and *T. trichiura* (eggs/g) by age group (median years).

Sources: (1) Needham et al. 1997; (2) Bradley and McCollough, 1973; (3) Needham et al. 1992.



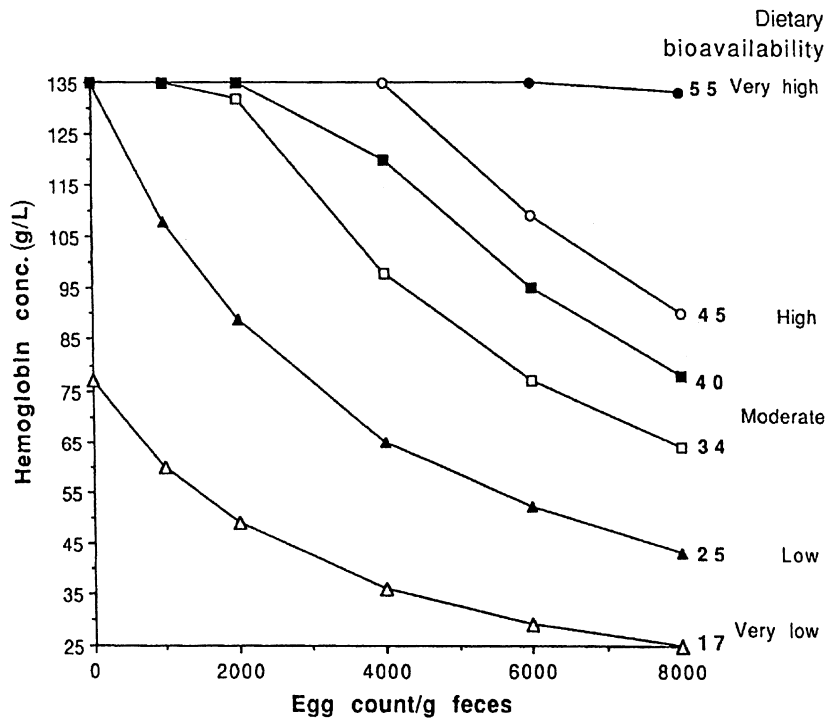
**Fig. 5:** Hookworm intensity by age in Zanzibar, Tanzania. Y axis values are geometric means of infected and uninfected people. Sources: Zanzibar preschool data: Stoltzfus<sup>3</sup>; Zanzibar school age data: Stoltzfus et al. 1997; Zanzibar adult data: Chwaya, unpublished data.<sup>4</sup>

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<sup>4</sup> H.M. Chwaya, Ministry of Health, Zanzibar, Tanzania.

(Bundy and Medley 1992). A hookworm infection of moderate intensity (2000–3999 eggs per gram feces) (Montresor et al. 1998) in a woman amounts to a daily fecal iron loss of 3.4 mg per day (Stephenson 1987). This compares with a physiologic basal iron loss in women of 0.77 mg/day (FAO/WHO 1988).

The interaction between hookworm load (i.e., fecal iron loss) and dietary iron bioavailability on hemoglobin concentration in women with no iron stores is illustrated in Fig. 6. This shows that, given a certain hookworm load (4000 eggs per gram), the impact on iron status will depend on the amount of iron available in the diet.



**Fig. 6:** Effect of different hookworm loads on hemoglobin concentration in women with median menstrual iron losses consuming diets with differing iron bioavailability. It is assumed that of the basal iron losses (14 µg/kg body weight), half is derived from losses of blood in the gastrointestinal and urinary tracts; bioavailability: micrograms of Fe absorbed per kilogram body weight per day in subjects with no iron stores. Source: Hallberg, unpublished.<sup>5</sup>

*Schistosoma hematobium* causes urinary iron loss which follows epithelial damage to the mesentery of the bladder and ureters (Stephenson 1987). A strong association has been found between urinary schistosomiasis and iron status in sub-Saharan Africa (Stephenson et al. 1985; Stephenson, Kinoti, et al. 1989; Greenham 1978). Stephenson et al. (1985) found that mean iron losses in children heavily infected with *S. hematobium* (208–1194 eggs /10 mL adjusted) was estimated to be 652 µg/day, an amount similar to average daily menstrual losses (Hallberg et al. 1966). *Trichuris trichiura* is associated with *Trichuris* dysentery syndrome, an intense colitis which results in iron loss from plasma and petechial hemorrhage (MacDonald et al. 1991).

**How much anemia is caused by hookworm?**

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In the context of a poor diet, hookworm-related blood loss contributes dramatically to anemia. Rates of anemia among children with heavy hookworm infection in Zanzibar were as high as 80% compared with 49% among noninfected children. The proportion of anemia associated with hookworm infection can be estimated by the attributable fraction. This is analogous to attributable risk, but the prevalence ratio of anemia in hookworm-infected versus uninfected individuals is used in place of a risk ratio. The attributable fraction estimates the proportion of anemia that could be prevented if hookworms were eradicated from the population (Kahn 1983). Applying this method to Zanzibari school-age children, 25% of all anemia, 35% of iron-deficiency anemia, and 73% of severe anemia were found to be attributable to hookworm infection (Stoltzfus et al. 1997) (Table 3). The same percentage of anemia (25%) was attributed to hookworm among Venezuelan school children where the hookworm prevalence was less, at

**Table 3: Attributable fractions (%) of anemia and severe anemia associated with hookworm infection in various populations.**

Population (N)	Hookworm prevalence (%)	Anemia (%)	Severe anemia (%)
<b>Zanzibar</b>			
Children			
4–29 months (263)	27	—	—
30–71 months (327)	69	13	49
Schoolers (3428)	94	25 (15–35)*	73 (35–110)
Nonpregnant women (582)	91	33 (7–59)	65 (–3–133)
Men (495)	95	40 (–1–81)	100
<b>Vietnam</b>			
Nonpregnant women			
Nationwide (5029)	37	15 (12–18)	
Central highland zone (743)	73	26	
Mekong river delta (719)	15	7	
<b>Venezuela</b>			
Children			
2–6 years (244)	55	17 (2–32)	
7–14 years (538)	78	25 (8–42)	
Women (222)	75	40 (12–68)	
Men (138)	84	20 (–37–77)	
<b>Nepal</b>			
Pregnant women (155)	77	4 (–14–22)	46 (16–76)

Note: Adapted from table provided by Stoltzfus (see footnote 3); this is a first attempt at determining attributable risk of anemia due to hookworms. Anemia is defined according to WHO cut-offs except for Zanzibar cut-offs which are 1 g/dL lower. Severe anemia defined as <7 g/dL in Zanzibar, <8 g/dL in Nepal. Zanzibar findings from Stoltzfus et al. (1997) and Stoltzfus, unpublished data (see footnote 3). Vietnam results from Report of the National Anemia and Nutrition Risk Factor Survey (1995).<sup>6</sup> Venezuela findings from Layrisse and Roche (1964) and Nepalese findings from Dreyfuss, Stoltzfus, et al. 1998.

\*95% confidence limits; confidence intervals in parentheses.

<sup>6</sup>Information on this report is available from the Centers for Disease Control and Prevention (CDC), Atlanta, GA USA.

**Table 4: Attributable fractions (%) of anemia and severe anemia associated with *S. hematobium* in African populations.<sup>a</sup>**

Population (N)	Schistosomiasis prevalence (%)	Anemia (%)	Severe anemia (%)
Niger, schoolers (174)	76	20 (-4-44)*	
Kenyan, school boys (136)	51		78 (59-97)
Gambia			
2-4 years (118)	16	—	
5-7 years (134)	43	34 (8-60)	
8-14 years (331)	71	43 (-14-100)	
15-44 years,			
Men (236)	62	42 (-3-87)	
Women (286)	30	—	
> 44 years, all (169)	7	2 (-16-20)	

<sup>a</sup> Table was prepared by Stoltzfus (see footnote 3) based on published data.

Note: Anemia defined as <12 g/dL, severe anemia defined as <8 g/dL in Kenya. Niger data from Prual et al. (1992); Kenyan data from Greenham (1978); Gambian data from Wilkins et al. (1985).

\* 95% confidence limits; confidence intervals in parentheses.

78%. In Zanzibar, there existed no threshold between intensity and anemia, unlike other populations in which there is a threshold (related to dietary iron factors). The threshold is related to the amount of body iron stores in the population: the higher the stores, the higher the threshold (Layrisse and Roche 1964). In a study of nonpregnant women in the central highland zone of Vietnam (see Table 3), 26% of all anemia was found to be attributed to hookworm where the prevalence of the latter was 73%. This compares with a 33% attributable fraction where hookworm prevalence was 91% among Zanzibari nonpregnant women. In Nepali pregnant women, however, only 4% of anemia (but 46% of severe anemia) was attributed to hookworm with a prevalence of 77%. Data on attributable fractions of anemia due to *S. hematobium* in African populations are presented in Table 4.

The attributable fraction is based on the prevalence of hookworm and the ratio of the prevalence of anemia in infected and uninfected individuals. The prevalence ratio will reflect the intensity of infections in the population and the iron stores of the population. However, an alternative approach would be to look at the attributable fraction of anemia due to hookworm for different categories of intensity of hookworm infection at different age and sex classes. The intensity of infections that can be experienced before the onset of anemia will depend on the iron balance of the individual (Crompton and Whitehead 1993), and this is related to age, sex, and diet. No agreement was reached on the most valid method of estimating attributable fractions of anemia associated with hookworm infection. Several concerns in using the attributable fractions were identified including:

- that the prevalence ratio may be biased if hookworm infected individuals have different iron intakes (or malaria risk or any other anemia-influencing factor aside from hookworms) and this would bias the attributable fraction;

- that the attributable fraction would overestimate what can be achieved by helminth control programs, since they typically reduce worm burdens by do not eradicate infections.

### Helminth control

Preventive measures to break parasite transmission include keeping feces out of the soil through using pit latrines, observing adequate hygiene and sanitation practices, and avoiding skin contact with soil (e.g., using footwear). Where hookworms are prevalent, hookworm control is a feasible and essential component of anemia control (see Table 5). Determination of fecal heme is noninvasive and may be a useful tool for measuring the impact of hookworm control activities (Stoltzfus et al. 1996a).

The Zanzibar studies showed that deworming at 4- or 6-monthly intervals was effective in reducing hookworm egg counts. Where transmission was very high, a 4-monthly interval regimen reduced hookworm egg counts significantly more effectively than the 6-monthly regimen (Albonico et al. 1998).

**Table 5: Results from controlled trials of antihelminthic treatment for hookworm infection: impact on hemoglobin levels.**

Country (study no.) <sup>a</sup>	Target population	Hookworm prevalence (%)		Impact on Hb <sup>b</sup>
		Initial	Final	
Kenya (1)	School age	83	53	+ 0.3 g/dL after 6 months*
Kenya (2)	School age	94	88	+ 0.3 g/dL after 8 months*
Kenya (3)	School boys	96	44	+ 0.4 g/dL after 4 months*
Zanzibar (4)	School age	96	88	+ 0.1 g/dL after 12 months
Papua New Guinea (5)	Men	100	3	+ 0.6 g/dL after 5 months*
India (6)	All	54	—	
	1–5 years			+ 0.5 g/dL after 6 months*
	6–14 years			+ 0.6 g/dL after 6 months*
	15–44			
	Men			+ 0.3 g/dL after 6 months
	Women			+ 0.2 g/dL after 6 months
Sri Lanka (7)	≥45 years			+ 0.5 g/dL after 6 months*
	Pregnant women	?	?	+ 2.5 g/dL in last half of pregnancy *

<sup>a</sup> (1) Stephenson et al. (1989); (2) Stephenson et al. (1985); (3) Stephenson et al. (1993); (4) Stoltzfus et al. 1998; (5) Shield et al. (1981), subjects were prisoners fed a healthy diet and protected from infection; (6) Report of the Working Group on Fortification of Salt with Iron (1982)—all individuals in the deworming trial had received iron-fortified salt for 6 months prior to deworming and throughout the deworming trial; (7) Atukorala et al. (1994)—all women received iron-folate tablets; they were not randomly allocated to anthelmintic treatment.

<sup>b</sup> Impact is defined as the pre–post difference in the treatment group minus the pre–post difference in the placebo group.

\*  $P < 0.05$ .

Treatment every 4 months has been the ongoing program since 1994 in Zanzibar, but cost effectiveness in this situation has not been measured. In other settings, annual treatment is sufficient, and even less frequent treatment is useful in some areas (Bradley et al. 1992).

Deworming does not get rid of all hookworms, so it will not achieve the type of impact suggested by the attributable risk fractions (for which the control group is people without any hookworms). Deworming only reduces iron loss through intestinal bleeding; it does not stop it. In areas of intense hookworm transmission, deworming at such intervals has been found to improve the iron status of school children (Stoltzfus 1998). Control of hookworm infection will have the greatest benefit for that segment of the population with moderate or severe anemia (Stoltzfus et al. 1997). In Zanzibar, 4-monthly school-based deworming was found to reduce the incidence of severe anemia (Hb < 7g/dL) by 55% (Stoltzfus et al. 1998).

Regarding the relative efficacy of different drugs in reducing hookworm infection, meta-analysis has confirmed that albendazole is more effective than mebendazole. The difference attenuates after 4 months. Both drugs are similarly and highly effective against *A. lumbricoides* and both are equally and modestly effective against *T. trichiura* (De Silva et al. 1997; Guyatt et al. 1993). No difference was found in the frequency of side-effects between the two drugs. Both drugs are available at similarly low or high cost in generic or proprietary form, respectively.

For *S. hematobium*, the dose of the drug of choice, praziquantel, needs to be related to the weight of the subject where high prevalences of hematuria related to *S. hematobium* are found. Fully detailed guidelines for its use in helminthic control measures (Montresor et al. 1998) and as a complement to iron supplementation are provided in the INACG publication (Stoltzfus and Dreyfuss 1998).

Deworming should be carried out among pregnant women after the first trimester when there is no risk of teratogenicity (WHO 1994). Deworming of pregnant plantation workers in Sri Lanka has been found to increase the beneficial effects of iron supplementation on hemoglobin concentration and iron status significantly (Atukorala et al. 1994).

Deworming has also been associated with improved growth among Kenyan school children (Stephenson, Latham, et al. 1989). However, the impact on the usual indicators of iron status may be attenuated due to the fact that growth is costly on iron (Stoltzfus et al. 1998). Although benefits nevertheless accrue, they might thus be more difficult to measure. In another study in South African 6–8 year olds, the individual and combined effects of iron-fortified soup consumption and deworming on iron status and growth were investigated (Kruger et al. 1996). Individually each intervention had an impact on iron status and growth, but the impact was greater when the interventions were combined.

These studies reinforce the need to obtain data on prevalence and intensity of parasitic infection and, where prevalences are greater than 20%, include anthelmintic therapy in anemia control strategies, particularly for school children and pregnant women. Periodic supervised deworming

1–3 times per year (depending on intensity) should be undertaken through the primary health care and school systems. Schoolchildren are usually a priority target group, and using schools for such treatment may have other positive benefits including possible incentives to enrolment and retention. Agencies advocating the school-based approach to deworming include WHO (Montresor et al. 1998) and UNICEF (Hall et al. 1997). Evidence of the practicality, cost, and effectiveness of this approach is given in Partnership for Child Development (1997).

## HIV/AIDS

### HIV infection and AIDS

Anemia is strongly associated with HIV infection, particularly in Africa. Anemia may be associated with the acquisition of HIV-infection (via blood transfusion), and HIV-infection may be a cause of anemia. Table 6 shows projections of peak HIV and AIDS incidences.

**Table 6: Epidemiological projections of peak HIV and AIDS incidence.<sup>a</sup>**

Continent	HIV		AIDS	
	Peak incidence per annum	Date	Peak incidence per annum	Date
Africa	1 million	Early 1990s	750 000	2005
Asia	1.3 million	2000	850 000	2010

<sup>a</sup> Source: Chin (1995).

Often the only life-saving treatment of severe anemia is blood transfusion. A high prevalence of HIV infection, which is especially high in malaria-endemic areas, means that the immediate benefit of blood transfusion has to be weighed against the risks of transmission of HIV by blood (see Table 7).

People at risk of HIV infection by blood transfusion in Africa include:

- children with malaria and anemia,
- women with pregnancy-related anemia or hemorrhage,
- victims of trauma,
- people with sickle-cell anemia, and
- a small number of hemophiliacs.

In 1 year (1985), 561 HIV-infected blood transfusions had been given to children (87% with malarial anemia) in one hospital (Fleming, 1997). Among women of child-bearing age ( $n = 3702$ ) in Kigali, seroprevalence has been found to be 45% among women who had been transfused and 28% among those never transfused (Fleming, 1997). In the past decade, the transmission of HIV through blood has been greatly reduced in Africa through the development of blood transfusion services and the strategies of voluntary donor selection and referral, and serological screening. There remain however many hospitals where these strategies are not applied, and a residual risk where they are practised successfully.

**Table 7: Association between blood transfusion and HIV in Kinshasa, Zaire, 1985.<sup>a</sup>**

Population	Number	HIV seroprevalence (%)	Previous blood transfusion	
			HIV-positive (%)	HIV-negative (%)
Children < 24 months, mothers HIV-negative	238	6.7	31	7
Children 2–14 years	368	10.9	60	33
Adult hospital workers	2387	6.4	9	5

<sup>a</sup> Sources: Mann, Francis, Davachi, Baudoux, Quinn, Nzilambi, Bosenge, Colebunders, Piot, et al. 1986; Mann, Francis, Davachi, Baudoux, Quinn, Nzilambi, Bosenge, Colebunders, Kabote, et al. 1986; Mann, J.M.; Francis, Quinn, et al. 1986.

### AIDS as a cause of anemia

Up to 70% of people with AIDS are anemic. The mechanisms include anemias of chronic disorders e.g. tuberculosis; HIV actions on stem cells and other precursors; an imbalance of growth factors due to HIV actions on macrophages, fibroblasts and T-cells; uncontrolled parvovirus B<sub>19</sub> infection; nutritional deficiencies including vitamin B<sub>12</sub>, folate, pyridoxine; over dosage with trimethoprim, pyrimethamine, antivirals; and anti-red cell antibodies (Bain 1997). Severe anemia in nonpregnant adults requiring admission to African hospitals is virtually all due today to the anemias of chronic disorders secondary to HIV and tuberculosis (Fleming 1998). In a recent Kenyan study, the attributable mortality fractions for severe anemia and HIV infection among women (*n* = 3466) of reproductive age were 31% and 75% respectively (Zucker et al. 1994). Anemia was found in 55% of these women and severe anemia (Hb < 6g/dL) in 6%. Severely anemic women were significantly more likely to be HIV positive (38% vs 17%) and more likely to die (10.7% vs 1.4%) than other women.

### Roles for antenatal clinics, obstetric, and gynecology service in AIDS control

Potential roles include:

- Serosurveillance.
- Identification, counseling, care and support of infected women and AIDS-affected families.
- Reduction of sexual transmission through education, control of other STDs, and condom distribution.
- Reduction of vertical transmission through contraception for HIV-positive women; condoms for HIV-negative, lactating women; vitamin A supplementation during pregnancy/lactation; antimalarial prophylaxis during pregnancy; antiretroviral therapy during pregnancy; termination of early infected pregnancies, avoiding traumatic delivery, vaginal lavage during prolonged labour; and elective caesarian sections for high risk mothers.

- Reduction of transmission by blood transfusion by appropriate use of blood; prevention of anemia; anticipation of difficult deliveries; prevention of postpartum hemorrhage.
- Prevention of nosocomial infections of patients and of health care workers.

## Hemoglobinopathies

### Sickle cell disease

Sickle cell disease is another consideration with respect to malarial infection and anemia control. Homozygous individuals are likely to die early, before adulthood. In heterozygotes, however, (referred to as having “sickle cell trait”), only about 40% of the hemoglobin is abnormal and this does not result in anemia. Such carriers of the trait are relatively protected from severe malaria, as the red blood cells containing hemoglobin S provide an environment that is hostile to the development and survival of *P. falciparum*. Up to 30% of adults in Africa are carriers and between 1–2% of infants are born with sickle cell disease (Nagel and Fleming 1992) (see Table 8). Individuals with sickle cell disease tend to have hemoglobin values of 6–10 g/dL. Sickle cell anemia is not very prevalent in adults due to the high mortality of such individuals during childhood; more subjects, however, are now receiving supportive care and as a result are reaching adulthood.

Among 98 pregnant women with sickle cell trait in a randomized, double-blind, placebo-controlled trial in the Gambia (19% of the 500 women in the trial), iron supplementation was found to be associated with a reduced hematological response, increased frequency of placental malarial infection and reduced birth weights on delivery (Menendez et al. 1995). Women without sickle cell trait on the other hand benefitted, with respect to iron status and birth weights, from supplementation.

**Table 8: Estimated frequencies and prevalence of sickle cell trait and disease.<sup>a</sup>**

Area	Sickle cell trait	Sickle cell disease
Tropical Africa	20–30%	130 000 infants per annum
India, Mediterranean, Americas, United Kingdom, etc.	<10%	30 000 infants per annum

<sup>a</sup> Source: Fleming 1998.

These findings suggest the need to screen women for sickle cell trait before iron supplementation, although no other studies have found this, and more are needed. Other studies have shown that *P. falciparum* parasitemias are less dense in primigravidae with sickle cell trait and that sickle cell trait protects against severe anemia in pregnancy associated with gross splenomegaly. The universal screening for sickle cell trait (and sickle cell disease) in pregnant women is feasible and has been practiced in some African centres for decades where hemoglobinopathies are prevalent. Ante-natal screening could lead on to screening of the infants of sickle cell trait mothers. The identification of neonates with sickle cell disease allows for early

and beneficial management.

## Thalassemias

The estimated frequencies and prevalences of various thalassemias are provided below:

### *Beta-thalassemias*

Asia:

Thalassemia minor*	150 million individuals
Thalassemia intermedias	40 000 infants per annum
Thalassemia major	50 000 infants per annum

\* Lowers hemoglobin by about 2 g/dL.  
(Fleming 1998)

Beta-thalassemias occur in high frequency in other populations including inhabitants of the Mediterranean basin, West Africa, and through migration, the Americas and the United Kingdom.

### *Alpha-thalassemias*

Asia and Oceania:

Asymptomatic*	< 80% populations
Hb H disease	60 000 infants per annum
Hb Bart's hydrops fetalis	20 000 infants per annum

\* Lowers hemoglobin by about 1 g/dL.

In sub-Saharan Africa up to 40% of the population has asymptomatic alpha-thalassemia. Thalassemia major and intermedia are iron-loading due to ineffective erythropoiesis (Weatherall 1995; Gillespie 1998). Iron fortification will not affect the outcome for such individuals. Iron supplementation will accelerate iron overload in undiagnosed beta-thalassemia major, but prognosis is already poor where medical services are undeveloped, and the ultimate outcome will not be materially affected. There is no contraindication to iron supplementation or fortification for heterozygous states of thalassemia as these do not represent iron-loading conditions.

## Outstanding issues

### *HIV*

There is an urgent need to develop blood transfusion services in Asian countries so as to reduce the transmission of HIV to a minimum; steps to be taken include:

- the formation of national policies;
- the establishment of services on a national basis with necessary legislation;
- the enforcement of minimal standards of blood-donor recruitment, selection, and care; blood storage, preparation, and laboratory procedures including serological testing;

- enshrinement of the principle of voluntary nonremunerated blood donation as the source of blood and blood products;
- the drafting of guidelines on the appropriate use of blood.

Transmission of HIV can be further reduced by the prevention of common and predictable situations where blood transfusion is required: public health measures include:

- malaria control,
- helminth control,
- prevention of nutritional anemias,
- improved prenatal care to anticipate hemorrhage,
- delayed first pregnancies and spacing subsequent pregnancies,
- the development of care for persons with sickle cell disease,
- the prevention of thalassemias (see below).

### ***Sickle cell disease in Africa***

The outlook for persons with sickle cell disease in Africa should be improved through:

- the establishment of neonatal diagnostic services,
- the practice of giving oral penicillin as prophylaxis against pneumococcal infections,
- the trial of new therapies, e.g., hydroxyurea.

### ***Thalassemias in Asia***

The burden of thalassemias in Asia can be reduced at present only through prevention of the birth of affected infants: there is the need to establish:

- programs for educating health care professionals, affected families, and the general public;
- population-screening programs;
- specialized diagnostic services for pre- and postnatal diagnosis;
- services for terminating pregnancies where fetuses are affected.

## **II: DETERMINANTS THROUGH THE LIFE CYCLE**

Following the discussion as presented in section I with regard to the determinants of anemia, factor by factor, the original plan for group work was to chart what this group knew about the relative contribution of each determinant to anemia in each region as a first step to identify gaps in knowledge and points of consensus. However the group decided that the best way to examine the determinants concurrently was to use a life cycle perspective, and for one region at a time because the pattern of determinants was quite distinctive by age and physiologic groups.

A matrix was developed by the group to illustrate which determinants were known to be important at different age/sex/physiologic groups in a specific region or subregion. The group developed the example shown in Table 9 which relates to sub-Saharan Africa. To indicate the process in generating the table, one subgroup of participants listed the determinants of anemia in infancy, a second subgroup focused on the preschool age, and so on. In plenary the chart was completed representing the best knowledge of the group. The group was satisfied that it identified all known causes of anemia by age for the sub-Saharan Africa region as a whole. However, the process made apparent how complex the interplay of factors was, and also how locally specific such a matrix could and should be. The same process used by this group could be used for other regions and more practically, subregions.

The group then was asked to identify the main determinant of anemia in each age group in rank order. From this multi disciplinary group there was considerable and rapid agreement on the relative contribution to anemia of each determinant at each stage of the life cycle, for this region. Table 9 indicates, by the number in brackets, the priority ranking of the contribution of the particular determinant to anemia. For example, in infants from birth to 1 year, dietary factors were ranked first or second depending whether malaria was endemic. If malaria was endemic, malaria was ranked first.

To make the process more generalizable, the steps in developing a useful matrix could be:

- 1) to determine the priority groups for anemia control based on the prevalence and severity of anemia in the age/physiologic group in the region;
- 2) to know the causes of anemia for each subgroup (with which this group had considerable expertise);
- 3) to rank the causes of anemia for each priority subgroup, recognizing that the relative importance of different causes will differ by subgroup.

Steps required but not well developed by this group would include:

- 4) identifying efficacious and cost-effective interventions for the priority causes;
- 5) integrating interventions for multicausal anemia and necessary complementary interventions (e.g., for malaria and iron deficiency).

The use of such steps and matrix could be applied in any given geographical situation, to identify and set priorities areas for action. For example, it might be decided that urgent action was needed to deal with the high levels of anemia in pregnant women and preschool children largely caused by dietary factors and malaria. There is a need to avoid over-compartmentalizing the problem when using the matrix. Interactions among different determinants and linkages between these determinants and anemia at different stages of the life cycle need to be kept clearly in sight.

To extend the above example—the way in which malaria and iron deficiency may coexist to precipitate severe anemia in a primigravida woman leading to the birth of a baby of low birth weight and with low iron stores is an example of both vertical and horizontal interactions in the matrix.

**Table 9: Life-cycle anemia risk matrix for sub-Saharan Africa.**

Determinant	Infant (0–1 year)	Preschool (1–5 years)	School-age (5–15 years)	Adolescent (12–19 years)	Reproduction-aged women 15–45 years)	Pregnant women	Adult men (≥20 years )
Diet	<ul style="list-style-type: none"> <li>• Iron content of complementary foods</li> <li>• Composition/ bioavailability</li> <li>• Lack of exclusive breast feeding (1 or 2)</li> </ul>	<ul style="list-style-type: none"> <li>• Iron content/ bioavailability of complementary foods</li> <li>• Continuity of breast-feeding (within 2<sup>nd</sup> year)</li> <li>• Content and bioavailability of family diet</li> <li>• Vitamin A? (1)</li> </ul>	<ul style="list-style-type: none"> <li>• Bioavailability (1)</li> </ul>	<ul style="list-style-type: none"> <li>• Bioavailability</li> <li>• High iron requirements</li> <li>• Iron density of diet</li> <li>• Seasonality (1)</li> </ul>	<ul style="list-style-type: none"> <li>• Bioavailability (1)</li> <li>• Increased iron demand</li> <li>• Folate (3)</li> <li>• Lactation may increase iron absorption ?</li> </ul>	<ul style="list-style-type: none"> <li>• Primigravidae (2) <ul style="list-style-type: none"> <li>-Low stores</li> <li>-High demand</li> <li>-Folate</li> </ul> </li> <li>• Multigravidae (1)</li> <li>• Inadequate intake and bioavailability (need for supplements)</li> </ul>	N/A
Malaria	<ul style="list-style-type: none"> <li>• Biggest cause of anemia (1 or 2)</li> </ul>	<ul style="list-style-type: none"> <li>• Diminishing with age as immunity acquire</li> <li>• Dependent on local transmission (2, but main cause of life-threatening anemia)</li> </ul>	-4	(4)	(5)	<ul style="list-style-type: none"> <li>• Primigravidae (1)</li> <li>• Multigravidae (2)</li> <li>• Cause of LBW and low iron stores in newborns</li> <li>• Seasonality</li> </ul>	<ul style="list-style-type: none"> <li>• Specific acquired immunity</li> </ul>
Helminths		<ul style="list-style-type: none"> <li>• Increasing problem, unknown scale in Africa (3)</li> </ul>	<ul style="list-style-type: none"> <li>• Hookworm (2)</li> <li>• Schistosomiasis increasing (3)</li> </ul>	<ul style="list-style-type: none"> <li>• Helminths &amp; <i>S. hematobium</i> (2) but little data on <i>S. hematobium</i> related to anemia</li> </ul>	<ul style="list-style-type: none"> <li>• Hookworm (3) but local transmission variation</li> </ul>	<ul style="list-style-type: none"> <li>• Hookworm (4) (regional differences)</li> </ul>	<ul style="list-style-type: none"> <li>• High risk occupations, esp farmers, miners (1)</li> </ul>
Genetic	<ul style="list-style-type: none"> <li>• Sickle cell disease (4) (1–2% newborns)</li> </ul>	<ul style="list-style-type: none"> <li>• Surviving sicklers (4)</li> </ul>	<ul style="list-style-type: none"> <li>• Sicklers diminishing (5)</li> </ul>			<ul style="list-style-type: none"> <li>• Sickle cell disease (5)</li> </ul>	
Other infections	<ul style="list-style-type: none"> <li>• Poor appetite, catabolic losses, raised requirements, AIDS</li> </ul>	<ul style="list-style-type: none"> <li>• Poor appetite, catabolic losses, raised requirements</li> </ul>		<ul style="list-style-type: none"> <li>• AIDS, TB (3) especially girls</li> </ul>	<ul style="list-style-type: none"> <li>• AIDS, TB and related infections (2)</li> <li>• HIV and malaria interaction</li> </ul>	<ul style="list-style-type: none"> <li>• AIDS (3)</li> </ul>	<ul style="list-style-type: none"> <li>• AIDS, TB, trauma, chronic infections (2)</li> </ul>
Other factors	<ul style="list-style-type: none"> <li>• Low birth weight</li> <li>• Maternal nutrition</li> </ul>			<ul style="list-style-type: none"> <li>• Excess blood loss</li> </ul>			

Note: Numbers in parentheses represent the group's priority ranking of the contribution to anemia of the determinant at each life-cycle stage, with 1 being most important and 5 being least important.

The matrix could be replicated for interventions, based on priority problems revealed, with key points relating to intervention feasibility including cost being listed in the boxes.

Participants identified the following possible uses for the matrix approach by decision-makers and program managers:

- to assess the degree of importance of the problem,
- to prioritize risk factors at district level,
- to prioritize interventions,
- as advocacy for anemia control,
- as an educational tool,
- to stimulate integrated disease control,
- to establish research priorities.

### **III: ASSESSMENT TOOLS**

Following the development of the matrix, the group decided that the next step would be to make the matrix as useful as possible for field officers, for example, to complete as an assessment tool. Specifically, the group was asked to:

- Describe the basic tools or methods for assessing the degree of contribution of a particular determinant to the problem of anemia.
- Describe the type of interventions are known to be efficacious in dealing with such determinant.
- Identify outstanding research questions.

The assessment tools and interventions identified by the participants are detailed in Table 10. The table lists some ideas that should be developed further. This exercise identified the need for simple epidemiological methods for assessing causes of anemia including methods for the whole range of causes.

### **IV: KNOWLEDGE GAPS AND RESEARCH PRIORITIES**

The group was finally asked to identify gaps in knowledge required to further improve the basis for anemia control. These research priorities were listed in general order of priority:

- to determine the efficacy of dietary modifications (bioavailability);
- to develop a database on iron bioavailability in foods;
- to determine the efficacy of antihelminthic treatment of pregnant women;
- to determine the effectiveness of antimalarial prophylaxes, particularly for pregnant women and infants;
- to determine the effectiveness of early malaria detection and prevention in reducing anemia mortality;

**Table 10: Assessment tools and relevant interventions to combat various determinants of anemia.**

Cause	Assessment tool	Intervention
Diet	<ul style="list-style-type: none"> <li>Assess anemia through hemoglobin and serum ferritin. (except ferritin in malarious areas)</li> <li>Dietary assessment of food patterns by food frequency, content of heme iron, inhibitors, enhancers; consumption of folate- and vitamin-A-rich foods; type and extent of processing of cereals and staples; type and extent of cooking, boiling, stir frying; use of iron pots; consumption of fortified foods</li> <li>Behavioural assessment of feeding practices and intrahousehold allocation of food</li> </ul>	<ul style="list-style-type: none"> <li>Supplementation (infants, cost, delivery, compliance, iron, multivitamins)</li> <li>Dietary modification (simple tips)</li> <li>Food fortification (commercial and home based)</li> </ul>
Malaria	<ul style="list-style-type: none"> <li>Assess using indicators of malaria's impact on anemia: <ul style="list-style-type: none"> <li>No. of transfusions (infants, young children, pregnant women)</li> <li>LBW or ratio of LBW in first pregnancy to LBW in subsequent pregnancies</li> <li>No. (and season) of hospital admissions, deaths, out patient visits for malaria</li> <li>on pilot survey basis, could do a placental malaria survey</li> <li>maternal deaths (related to severe anemia)</li> <li>community perception of malaria as a problem</li> <li>spleen size (bigger spleen, the greater the anemia)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>For infants and pregnant women, prevention (bednets, prophylaxis, need to specify best regimen), and treatment</li> </ul>
Intestinal helminths	<ul style="list-style-type: none"> <li>Divide communities into ecological zones. Survey third graders by Kato-Katz and reagent strips for hematuria, as per WHO guidelines. Categorize by prevalence and intensity (WHO/CTD/SIP/98.1 cited in Montresor et al 1998). In problem zones, survey X preschoolers and adult women to identify high risk groups</li> </ul>	<ul style="list-style-type: none"> <li>Deworming regimes, as per WHO (Montresor et al. 1998)</li> </ul>
Genetic	<ul style="list-style-type: none"> <li>For sickle cell disease, do adult population prevalence survey based on Hb electrophoresis which will provide data on sickling gene frequency; then calculate genotype distribution in population</li> <li>Numbers count in hospital, pilot survey</li> </ul>	<ul style="list-style-type: none"> <li>Antimalarial prophylaxis (bednets, drugs)</li> <li>Education of patient and parents to prevent sickle cell crisis</li> <li>Folic acid supplementation (short term iron supplementation is not a problem), nutritional advice</li> <li>Regular clinic attendance, report when ill or pregnant</li> <li>Supervision of pregnancy, delivery, puerperium</li> <li>Family limitation to 3 surviving children</li> </ul>
Other infections	<ul style="list-style-type: none"> <li>AIDS: <ul style="list-style-type: none"> <li>prevalence by annual surveys in antenatal clinics for HIV</li> <li>calculate rate of vertical transmission to children and mother/fetus ratio</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Reduce vertical transmission (mother to child) by vitamin A supplementation (? research question) and affordable antivirals (AZT)</li> <li>Malaria prophylaxis in pregnancy</li> <li>Others, e.g., avoid traumatic delivery</li> </ul>

- to document the impact of cost-effective anemia-control package on pregnant women and children (i.e., process and outcome of anemia-control programs);
- to investigate alternate (and combination) deworming drug regimens;
- to assess post-malarial intervention on morbidity and mortality;
- to determine the cost-effectiveness of various anemia-control packages;
- to assess the interaction of HIV and malaria in pregnancy (role of anemia and possible vertical transmission);
- to assess the relationship of vitamin A on HIV/AIDS transmission;
- to study the interaction of vitamin A and iron on iron status and anemia;
- effectiveness of antihookworm interventions (i.e., which hookworm interventions are most effective).

## V: CONCLUSIONS

Anemia has a multifactorial etiology and the contributions of its determinants vary in many ways. Anemia can be caused by dietary factors, malaria, intestinal parasites, HIV, or certain genetic hemoglobinopathies. Geography, ecology, age, sex, and physiology are just some of the main factors that condition the degree to which any one of these determinants affects the anemia outcome. Moreover determinants interact.

Participants have attempted to identify the nature of anemia's determinants and their interrelationships. The participants have used a simple process for looking at all determinants with a view to ultimately improving the basis for choosing anemia control strategies. The life cycle anemia risk matrix can be used to view determinants with respect to different age, sex, and physiologic subgroups of the population and to aid in prioritizing target groups and interventions.

As an exercise to consider all causes of anemia concurrently throughout the life cycle, the example of sub-Saharan Africa was used. The following summarizes the general conclusions from the exercise:

- The most important determinant of anemia at every stage in the life cycle, except pregnancy and infancy, was found to be the diet, particularly bioavailability of iron.
- In pregnant women, malaria was the main determinant of anemia in malarious areas for primigravidae, and both inadequate iron intake and bioavailability were the main determinants in multigravidae.
- Malaria and diet were the main determinants of anemia in infants in the first year of life.
- Intestinal helminths were the third ranked determinant for school-aged children and adolescents and fourth for pregnant women.
- Intestinal helminths were ranked as the number one determinant for adult men in high risk occupations such as farming.

This exercise was successful in identifying how complex such a matrix of causes is, and how locally specific it must be. The matrix can be a useful tool in identifying priority groups for

anemia control, when anemia prevalence and severity are known, by age and sex group, and causes and their relative contribution to anemia are known. The need for simple epidemiological methods for assessment of multiple determinants was identified as well as promising tools for further development.

Participants also identified important knowledge gaps and stressed the need to investigate multiple causes with a view to maximizing the potential of integrated approaches to anemia control.

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## Appendix

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### Expert Consultation on Anemia Determinants and Interventions

*Hosted and Sponsored by the Micronutrient Initiative*

*September 16–17, 1997, Ottawa, Canada*

#### Tuesday, 16 September

Chair of Meeting: Rebecca Stoltzfus

Facilitator: Bill Staples

8:30	Welcome: M.G. Venkatesh Mannar Opening remarks: Judith McGuire Introduction of participants Objective and expected outputs:Chair
9:00	Brief updates by identified participants. Individual presentations will focus on: 1) the main association between particular determinant and anemia; 2) the type of variations (geographical, ecological, socioeconomic, age, sex, etc.) in the strength of this association viz-à-viz other factors; 3) what do we know of the efficacy and effectiveness of the main interventions for reducing the effect of this determinant; and 4) what do you feel are the key remaining issues to be resolved in order to improve action for anemia prevention and control.  15-min presentations each followed by 10 minutes of initial focussed discussion.  Diet and anemia: Stan Zlotkin Malaria and anemia: Bernard Brabin
10:00–10:15	Break  Intestinal parasites and anemia: Rebecca Stoltzfus Other factors (including hemoglobinopathies and HIV): Alan Flemming
12:00	Lunch
13:00–17:30	In-depth discussion on relationships between determinants efficacy and effectiveness : Bill Staples, Facilitator
13:15	Diet and anemia
14:00	Malaria and anemia
14:45	Parasites and anemia
15:30	Other factors (including hemoglobinopathies and HIV) and anemia
16:15–16:30	Break
16:30	Important interactions
17:30	Close
18:00	Reception hosted by the MI-14th floor IDRC

## Wednesday, 17 September

8:30	Remaining issues/gaps re: 1) etiology 2) efficacy and effectiveness of interventions Options for becoming more effective in actions for anemia prevention and alleviation
10:00	Break
10:15	Workshop on developing key elements of consensus on anemia determinants, alleviation, and prevention
12:15	Lunch
13:15	Remaining issues re: policies and programs: What interventions should be pursued under what conditions? What are the implications for programming, advocacy and mobilization? Consensus on appropriate and sustainable integration?
14:30	Next steps
15:00	Close of meeting

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