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Iron-Deficiency Anemia: Reexamining the Nature and Magnitude of the Public Health Problem

An Analysis of Anemia and Child Mortality[1,2]

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ABSTRACT   The relationship of anemia as a risk factor for child mortality was analyzed by using cross-sectional, longitudinal and case-control studies, and randomized trials. Five methods of estimation were adopted: *1*) the proportion of child deaths attributable to anemia; *2*) the proportion of anemic children who die in hospital studies; *3*) the population-attributable risk of child mortality due to anemia; *4*) survival analyses of mortality in anemic children; and *5*) cause-specific anemia-related child mortality. Most of the data available were hospital based. For children aged 0–5 y the percentage of deaths due to anemia was comparable for reports from highly malarious areas in Africa (Sierra Leone 11.2%, Zaire 12.2%, Kenya 14.3%). Ten values available for hemoglobin values <50 g/L showed a variation in case fatality from 2 to 29.3%. The data suggested little if any dose-response relating increasing hemoglobin level (whether by mean value or selected cut-off values) with decreasing mortality. Although mortality was increased in anemic children with hemoglobin <50 g/L, the evidence for increased risk with less severe anemia was inconclusive. The wide variation for mortality with hemoglobin <50 g/L is related to methodological variation and places severe limits on causal inference; in view of this, it is premature to generate projections on population-attributable risk. A preliminary survival analysis of an infant cohort from Malawi indicated that if the hemoglobin decreases by 10 g/L at age 6 mo, the risk of dying becomes 1.72 times higher. Evidence from a number of studies suggests that mortality due to malarial severe anemia is greater than that due to iron-deficiency anemia. Data are scarce on anemia and child mortality from non-malarious regions. Primary prevention of iron-deficiency anemia and malaria in young children could have substantive effects on reducing child mortality from severe anemia in children living in malarious areas.   J. Nutr. 131: 636S–648S, 2001.

KEY WORDS: • *children* • *anemia* • *mortality* • *malaria* • *iron deficiency*

Anemia prevalence in children is high, especially in developing countries (DeMaeyer and Adiels-Tegman 1985) and frequently is multifactorial. It is often associated with childhood malnutrition, producing interlinked factors, several of which could be causally related to mortality risk. These factors include lack of hematinics (e.g., iron, folate, vitamins A, B-12 and C, and copper), impairment of red cell production by acute or subacute inflammation (with an increase in stored iron) and increased red cell destruction either via specific infections (e.g., malaria) or specific nutrients (e.g., vitamin A). How is anemia associated with these factors related to child mortality? Is there a hierarchy of importance? What mechanisms could lead from these nutrient deficiencies, especially iron deficiency, to higher mortality? Although there is a sense that severe anemia will increase mortality risk, how substantial is the evidence related to mild or moderate anemia?

The purpose of this analysis is to review the contribution of iron-deficiency anemia to child mortality and to estimate the magnitude of that effect. In view of the above framework, an analysis of this nature is limited in the absence of an appropriately defined hypothesis (Palloni 1987). Iron-deficiency anemia could interact with mortality in several ways, some of which may even be advantageous (Bullen and Griffiths 1999). The proposition that childhood anemia increases mortality risk is open to evaluation mainly through cross-sectional and case-control studies, and the data available have not been derived on the basis of testing established hypotheses. For example, analysis of the National Nutrition Status Survey of Zambia identified significant interactions between the hemoglobin (Hb)[4] level of the youngest child in a family with the

[4] Abbreviations used: CI, confidence interval; Hb, hemoglobin; OR, odds ratio; PAR, population-attributable risk; RR, relative risk.

social factors associated with child death rates (e.g., intertribal marriage or lack of parental education), but the mechanisms governing these associations were unknown (Wenlock 1979).

Only one intervention study includes an evaluation of infant mortality in relation to iron supplementation (Alonso-Gonzalez et al. 2000). Additional trials with mortality outcomes, from trials in toddlers with iron-deficiency anemia to preventive trails in younger infants to trials in school children with iron-deficiency anemia, have not been identified (S. Logan, Institute of Child Health, London, personal communication). Within the framework of these limitations, the methods adopted in this analysis of anemia as a risk factor for child deaths include the following: *1*) the proportion of child deaths attributable to anemia; *2*) the proportion of anemic children who die in hospital studies; *3*) the population-attributable risk of child mortality due to anemia; *4*) survival analyses of mortality in anemic children; and *5*) cause-specific anemia-related child mortality.

METHODS

Identification of published studies. Published studies on the relationship between anemia (defined by severity) and childhood mortality were identified using Medline, references in published papers, Cochrane Review issues and personal communications. Only hospital or community studies in developing countries were considered.

Selection of studies for inclusion in the analyses. Studies identified were reviewed with regard to the following factors: ages of children (up to 12 y), anemia severity, clinical presentation data, use of blood transfusion, length of follow-up, etiological diagnosis, laboratory estimation of Hb or hematocrit, and analytical methods. Hematocrit was converted to a Hb value by dividing by 3 and multiplying by 10. Studies stating that anemia was a direct cause of death were of particular value, permitting the estimate of the total number of child deaths attributed to anemia. Of the studies identified, 10 provided data for which Hb midpoint values could be calculated. All other studies used anemia cut-off points below which proportional groups of children with anemia were defined.

Definitions. Mild anemia was defined as Hb <110 g/L, moderate anemia as <70 g/L and severe anemia as <50 g/L. The 110 g/L cut-off value is based on international convention, whereas the other two cut-off values are commonly used in the literature.

Analyses. For each of the studies selected, estimates of the relative risks (RR) and their 95% confidence intervals (CI) were calculated using established methods (Kleinbaum 1982). Several case fatality studies could not be used in the risk analysis because they did not present mortality data for the less anemic subjects in their study population. Because the greatest number of studies were stratified by Hb <50 g/L, this criterion was used for inclusion of individual studies in pooled analyses.

Relative risk values were estimated and the relationship between anemia severity and mortality risk was analyzed by curve fitting (linear, quadratic, exponential) and coefficients of determination (R^2 values) were calculated. These were used with prevalence estimates to obtain the population-attributable risk (PAR) of anemia-related child mortality as follows:

$$\text{PAR} = \text{deaths related to anemia/total deaths}$$
$$= [\text{Prev} \times (\text{RR} - 1)]/\{1 + [\text{Prev} \times (\text{RR} - 1)]\}$$

where Prev is the prevalence of anemia and RR is the ratio of mortality in anemic subjects to mortality in less anemic subjects.

Results from an iron supplementation and malaria chemoprophylaxis trial reported by Menendez et al. (1997) and the prospective descriptive study by Zucker et al. (1996) were used to estimate years of life lost because of anemia related to iron deficiency, malaria and other causes.

TABLE 1

Estimated anemia deaths (in thousands) in children[1]

	Males		Females	
Region	0–4 y	5–14 y	0–4 y	5–14 y
Developed (all)	—	—	—	—
Developing (all)	19.9	6.0	16.2	23.0
Established market economies	—	—	—	—
Formerly socialist economies	—	—	—	—
India	6.4	1.3	5.3	7.2
China	1.6	—	4.8	2.3
Other Asia and islands	2.9	1.2	1.4	4.6
Sub-Saharan Africa	4.3	1.1	1.9	4.9
Latin America and Caribbean	1.5	—	1.1	—
Middle Eastern crescent	3.3	—	1.8	3.3
World	20.1	6.2	16.4	23.2

[1] Source reference: Murray and Lopez (1994). A dash (—) indicates <1000 deaths.

RESULTS

The proportion of child deaths attributable to anemia

Anemia is now recognized as an important cause of morbidity and mortality in African children admitted to hospitals but is rarely cited as a cause of death outside hospitals (Awashi and Pande 1998). This is probably because the diagnosis of anemia by verbal autopsy and morbidity interviews in the community is unusual and unreliable (Alonso et al. 1987, Belcher et al. 1976). In a prospective study in the Gambia, the sensitivity, specificity and predictive value of verbal autopsy interviews for anemia compared with hospital-derived diagnoses were 33, 98 and 50%, respectively (Snow et al. 1992). The pattern of deaths attributable to anemia will also vary by child's age because clinical severity is greater in young children (De Maeyer and Adiels-Tegman 1985, Le Cessie et al., unpublished data, 2000). Epidemiologic studies in the Gambia have shown that the marked seasonal variations that occurred in clinical malaria and malaria parasitemia were associated with similar variations in the prevalence and severity of childhood anemia (McGregor et al. 1966). Furthermore, peak mortality in young children occurred seasonally when malaria and anemia were most prevalent (Ian McGregor, personal communication).

Table 1 shows the number of deaths attributed to anemia (all forms) in hospital and nonhospital settings summarized by the Global Burden of Disease Group and published by the World Health Organization (Murray and Lopez 1994). The greatest burden is in females in developing countries, and regionally the highest estimates are for India and then sub-Saharan Africa. Younger males and older females are at highest risk of death.

Table 2 shows the proportion of deaths related to anemia for several African and one Indian report. All are hospital based except the study from Zaire, which was a prospective rural community study in a random cluster sample of 5167 children. All are from malarious areas, except for the study from Agra in India, which attributed only 2% of admissions and 0.2% of deaths to malaria. For children 0–5 y of age, the percentage of deaths due to anemia is similar for reports from highly malarious areas, i.e., Sierra Leone (11.2%), Zaire (12.2%) and Kenya (14.3%). These estimates are higher than those for children <5 y old from urban Kampala, where malaria transmission is not intense. A lower proportion of

TABLE 2

Anemia as a cause of death in children in developing countries

Country	Type of study	Years	Age group	Deaths	Anemia as a cause of death[1]	Reference
				n	*n (%)*	
Uganda (Kampala)	Retrospective hospital and autopsies	1967–68	1–12 mo	224	15 (6.7)	Bwibo 1970
			1–5 y	372	30 (8.1)	
			All ages	871	53 (6.1)	
Sierra Leone (Freetown)	City death registry	1969–79	1–4 y	3825	176 (4.6)	Kandeh 1986
		1987–91	0–12 mo	2419	193 (8.0)[2]	Hodges and Williams 1995
			0–5 y	1845	285 (15.4)[2]	
India (Agra)	Retrospective hospital admissions	1969–78	0–5 y	1327	51 (3.8)	Kalra et al. 1988
Zimbabwe (Harare)	Retrospective hospital admissions	1982	1 mo–8 y	349	10 (2.9)[2]	Chawla and Haufton 1988
Zaire (Bwamanda)	Prospective community	1989–91	0–5 y	246	30 (12.2)[2]	Van Den Broeck et al. 1993
Ghana (Accra)	Prospective hospital emergency room	1991	1–12 y	446	259 (58.1)[3]	Commey and DeKyem 1995
Kenya (Siaya)	Prospective hospital	1991	<5 y	265 (with follow-up)	86 (32.4)[2,4]	Zucker et al. 1996
				265 (no follow-up)	38 (14.3)	
Malawi[5]	Prospective hospital					
Mangochi		1990–91	0–10 y	458	43 (9.4)	Slutsker et al. 1994
Blantyre		1990–91	0–10 y	1194	77 (6.4)	
Gambia	Prospective hospital	1989–91	1 mo–11 y	152	7 (4.6)	Snow et al. 1992

[1] Severity not defined unless stated.
[2] Anemia as primary diagnosis of cause of death.
[3] Hb <70 g/L, none transfused.
[4] Hb <50 g/L.
[5] Excluded cases of cerebral malaria.

deaths was attributed to anemia when children >5 y old were also included, i.e., 6.1% in Uganda and 2.9% in Zimbabwe. Only two of these studies reported anemia-related infant deaths (4.0% in Uganda and 8.0% in Sierra Leone) (Bwibo 1970, Hodges and Williams 1998), which were less frequent than in children 1–4 y old.

In Kenya, the risk of dying was associated with age and Hb level. Children who died were significantly younger (mean $\pm$ SD = 9.6 $\pm$ 10.2 vs. 13.4 $\pm$ 10.6 mo, $P < 0.0001$). The lowest risk of death from anemia was found in the two areas with little malaria exposure (Agra, India, and Harare, Zimbabwe). The highest risks occurred with nontransfused pediatric emergency admissions (58.1%) and in a prospective follow-up study of a cohort of children, many of whom had chloroquine-resistant malaria (Commey and DeKyem 1995, Zucker et al. 1996).

Three of these reports specify the causes of the anemia-related deaths (**Table 3**). Malaria-attributable anemia occurs in a similar proportion for the Kenyan and Ghanaian studies (12.2 and 12.6%, respectively). Hospital deaths due to anemia in Kenya would be expected to be much higher than those in Ghana, where chloroquine resistance is much lower. Nutritional anemia is the predominant cause in the Ghana series and hookworm anemia is predominant in the Ugandan series (30.2 and 5.7%, respectively).

Within the National Health Management and Information System in Tanzania, anemia is responsible for 17.8% deaths in hospitalized children <5 y of age. It is the second cause of death after malaria, and the pattern of child deaths attributable to anemia changes with malaria transmission. In areas in which malaria transmission is high (holoendemic), the anemia-attributable deaths increase. Observations in pediatric wards also reveal that the number of blood transfusions given increase during the peak malaria season.

The data from Tanzania and the hospital-based data presented in Table 2 regarding anemia as a cause of death in children in developing countries are convincing on two points, i.e., anemia is now recognized as an important cause of morbidity, and mortality and the association of anemia with malaria epidemiology appear to be quite significant

The proportion of anemic children who die

Table 4 summarizes 14 studies reporting case fatality rates for anemic children. Most children were < 5 y of age and only one study included neonates. All were from intermediate- to high-transmission malarious areas of Africa except for the report from Madang, Papua New Guinea, which is also a malarious area. Treatment schedules varied substantially among these studies, with the percentage receiving transfusion ranging between 0 and 100%. Across the 11 study groups that reported the proportion of children transfused, no association was found between case fatality rate and the percentage of children transfused (**Fig. 1**). Lackritz et al. (1992), in a detailed study from Kenya reported that only children whose Hb was < 39 g/L and who were transfused had lower mortality than those not transfused. Above this level, transfusion was of little benefit. This was not a randomized trial. The review of Meremikwu and Smith (1999) of blood transfusion for treating malarial anemia concluded that there was insufficient data to determine whether routinely giving blood to clinically stable children in endemic malarious areas, with severe anemia and no respiratory distress, reduced death or results in higher hematocrit measured at 1 mo.

No information was provided on the prevalence of iron-deficiency anemia in these studies. Bojang et al. (1997) excluded children with sickle cell disease, severe malnutrition or hemorrhage. Details of malaria parasitemia were available for

TABLE 3

Primary diagnosis of anemia-related deaths in children[1]

Diagnosis	Cause of anemia related death	Type of study	Reference
	n (%)		
Kenya			
(deaths *n* = 254)			
Malaria	31 (12.2)	Prospective hospital	Zucker et al.
Bacteremia	22 (8.7)	(admission and	1996
Malnutrition	2 (0.8)	postdischarge	
HIV infection	3 (1.2)	follow-up; <5 y)	
Diarrhea	0 (0.0)		
Pneumonia	6 (2.4)		
Febrile illness	6 (2.4)		
Symptomatic	9 (3.5)		
anemia	0 (0.0)		
Measles	2 (0.8)		
Chronic diarrhea	81 (32.0)		
All			
Ghana			
(deaths *n* = 259)			
Nutritional anemia	135 (52.1)	Pediatric emergency	Commey and
Severe malaria	56 (21.6)	room (1–12 y)	DeKyem
Sickle cell anemia	28 (10.8)		1995
PEM	22 (8.5)		
Gastroenteritis/	18 (6.9)		
pneumonia/meningitis			
Uganda			
(deaths *n* = 596)			
Hookworm anemia	34 (5.7)	Retrospective	Bwibo 1970
Sickle cell anemia	11 (1.8)	hospital (1 mo–5 y)	

[1] HIV, human immunodeficiency virus; PEM, protein-energy malnutrition.

several reports because inclusion criteria depended on the presence of parasitemia (Bojang et al. 1997, Brewster and Greenwood 1993, Schellenberg et al. 1999, Slutsker et al. 1994). Two studies included only anemic children with malaria parasite densities >10,000/μL (Allen et al. 1996, Marsh et al. 1995).

Midpoint Hb values were available for 10 of these reports. The regression of case fatality rates against midpoint values showed no significant association with case fatality rates. The best line fit was for a quadratic curve that was U-shaped (R^2 = 19.6%, P = 0.316) (**Fig. 2**). The highest case fatality was 41.4% for the midpoint Hb value of 37 g/L (Lackritz et al. 1997).

The association of case fatality rates with anemia cut-off points is shown in **Figure 3**. This analysis includes additional studies that did not provide Hb midpoint values. The association remains nonsignificant with a best line fit for a logarithmic curve (R^2 = 12.2%; P = 0.203). Hemoglobin and case fatality are negatively correlated. The values available for Hb <50 g/L showed a variation in case fatality from 2 to 29.3%. Despite these differences, similarities exist among observations from the same countries. For example, the three studies from Tanzania show low case fatality between 2 and 7% (Holzer et al. 1993, Schellenberg et al. 1999, Van Hombergh et al. 1996). In the Gambia, risk was higher but similar in the two studies from Banjul (9.6 and 13.3%) (Bojang et al. 1997, Brewster and Greenwood 1993). In contrast, in Kenya, low risk was reported in Kilifi in a research setting (Marsh et al. 1995) but was much

higher in Siaya in the context of routine hospital management (Lackritz et al. 1992, Zucker et al. 1996). The proportion of children with sickle cell disease is likely to explain some of this variation. The pattern of association of Hb with case fatality is similar in Figures 2 and 3 except that when the midpoint Hb value is used, case fatality is higher in the most anemic children.

The data provided by this analysis suggest little, if any, dose response relating increasing Hb level (whether by mean value or selected cut-off values) with decreasing mortality. This lack of a dose-response relationship may be a function of the limited range of Hb values in the populations reported. Most of these studies are based on children admitted to hospitals, with admission possibly dependent on their Hb level. This selection makes it difficult to compare mortality experience internally or externally to a group of children with better iron status but equivalent comorbidity and underlying risk of death.

Population-attributable risk of child mortality due to anemia

Table 5 compares the RR of mortality in anemic children with their less anemic counterparts (RR A) and with the least anemic referent group available across all studies (RR B). Regression analysis showed no association between the values for RR A and Hb cut-off values (R^2 = 5.0%; P = 0.74). This may result because the risk of death is still substantial in the less anemic groups. The most frequent cut-off value for anemic children was <50 g/L. The pooled Mantel Haenszel weighted RR for the six studies with this anemia cut-off value was 1.92 (95% CI: 1.69–2.18), indicating a substantially increased risk of death in severely anemic children.

Figure 4 shows the logarithmic regression of Hb cut-off points against RR B. There is an increased risk of death in children with Hb values <80 g/L. The association does not reach statistical significance (R^2 = 13.8%; P = 0.156). This arises in part because of low mortality (<2%) in three studies (Allen et al. 1996, Bojang et al. 1997, Holzer et al. 1993). These were from centers with active research groups offering greater staff support for optimal management. Of the 16 studies available for calculation of RR B, 12 showed significantly increased risk ratios. Those with nonsignificant values had smaller sample sizes. In the two reports from Siaya, Kenya, severely anemic children showed a 12-fold increased mortality risk. The Mantel-Haenszel weighted RR for the 10 studies using the <50 g/L cut-off value was 6.07 (95% CI: 5.2–7.1). However, the RR of mortality (Fig. 4) for the Hb cut-off value of <50 g/L shows extreme variation. The wide variation among the different studies is likely related to methodological variation, thus placing severe limits on causal inference. Given the general weakness in the causal evidence relating most iron-deficiency anemia in young children to mortality, it is premature to generate projections regarding population-attributable risk. However, such estimates, based on the risk values in this analysis, would be substantial.

From a public health point of view, it is necessary to know the risk factors in the different studies for developing severe anemia. Studies along the coast of Tanzania have identified fever, parasitemia and age of the child as predictive factors for anemia (Premji et al. 1995). Hedberg et al. (1993) also showed that the population-attributable risk and OR for factors associated with anemia requiring hospitalization were also significant for low socioeconomic status and malnutrition. Evidence from population-based studies in Tanzania and the Gambia on malaria control in relation to change in Hb values and child mortality after community interventions were also reviewed

TABLE 4

Childhood hemoglobin (Hb) levels and case fatality

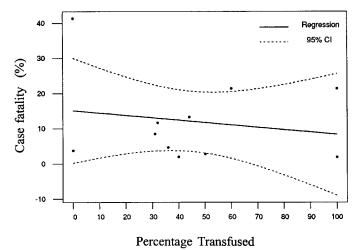| Year	Location	Age	Hb	Deaths	Survivors	CFR[1]	Transfusion	Reference
			g/L	n	n	%	%	
1991	Kenya (Siaya)	<5 y	<50	86	207	29.3		Zucker et al. 1996
			>50	179	751	19.2		
1989–91	Kenya (Siaya)	<12 y	<39	56	118	32.2	60	Lackritz et al. 1992
			<50	33	209	21.3		
			>50	136	1499	8.3		
1991	Kenya (Siaya)	<5 y	<50	40	147	21.4	100	Lackritz et al. 1997
			<50	48	68	41.4	0	
			>50	59	244	19.5		
1989–91	Kenya (Kilifi)	<4 y	<50	15	305	4.8	36	Marsh et al. 1995
1989–91	Kenya (Kilifi)	0–5 y	<50	13	146	8.2	31	Newton et al. 1997
			<50	11	110	9.1		
			>50	100	1960	4.9		
1989	Tanzania (Ifakara)	2 mo–6 y	<60	1	51	1.9	100	Holzer et al. 1993
			<60	2	31	3.8	0	
1995–96	Tanzania (Ifakara)	1–7 mo	<50	4	80	7.0		Schellenberg et al. 1999
			<80	9	285	3.1		
			>83	6	237	1.7	>8	
		8 mo–4 y	<50	4	87	4.4		
			<80	19	474	3.9		
			>83	24	974	2.4		
1993	Tanzania (Turiani)	<30 mo	<50	2	98	2.0	40	Van Hombergh et al. 1996
1991	Ghana (Accra)	1–12 y	<70	259	2212	11.7	32	Commey and KeKyem 1995
			>70	187	8995	2.1		
1990–94	Zambia (Macha)	5 mo–6 y	60 (mean)	39	183	17.6		Mabeza et al. 1998
			92 (mean)	5	64	7.2		
1990–95	PNG (Madang)	0.2–12.4 y	<50	3	100	2.9	Most transfused	Allen et al. 1996
			>50	14	361	3.7		
1990–91	Malawi (Mangochi) (Blantyre)		<50	57	348	14.0		Slutsker et al. 1994
			<50	84	428	16.4		
1993–94	Gambia (Banjul)	6 mo–9 y	<40	23	150	13.3	44	Bojang et al. 1997
1988–90	Gambia (Banjul)	<12 y	<60	101	949	9.6		Holzer et al. 1993

[1] CFR, case fatality rate.

(Alonso et al. 1993, Bradley 1991). These studies reported mean hematocrit (or packed cell volume) and not prevalence of anemia, which restricted their use for estimation of attributable risk. Nevertheless, with reductions in malaria transmission through vector control or use of insecticide-impregnated bed nets, substantial reductions in child mortality (in children <5 y old) occurred (almost halved), which paralleled significant improvements in mean hemoglobin values.

Survival analysis in anemic children

Low birth weight is a strong predictor of mortality, and low-birth-weight babies are also at greater risk of developing anemia during infancy (Murray and Lopez 1994, Verhoeff et al., unpublished, 2000). It has recently been recognized that fetal anemia (cord Hb <125 g/L) occurs frequently in developing countries (Brabin 1992). Postneonatal infant mortality in Malawi has also been related to fetal anemia and low birth weight. In an infant cohort study of 92 infants with low birth weight, 120 with fetal anemia and low birth weight, and 188 with neither, those with fetal anemia and low birth weight had the poorest survival (Verhoeff 2000). In this context, being anemic at a young age reflects previous morbidity. This is compounded by exposure to infection, which further increases risk of anemia because sick children do not absorb iron well (Bullen and Griffiths 1999). Furthermore, children who become ill (e.g., from diarrhea) are likely to have repeated or persistent episodes that may make them more at risk of anemia. In Brazil, anemic children were more likely to have had diarrhea than nonanemic children, and diarrhea was a predictor of anemia in a multiple regression analysis (Ann Hill, personal communication).

Figure 5 shows the results for a community cohort of 216 Malawian infants who had Hb values taken at 6 mo and who did not receive iron supplements before 6 mo. The details of the pattern of anemia in these infants has been reported by Le Cessie et al. (unpublished data, 2000). There were 31 infants who died who had at least one Hb measurement. The curves are estimated from a Cox regression model and the Hb value is entered in this model as a continuous variable. The estimated hazard ratio was 0.581 (95% CI: 0.379–0.888), indicating that if Hb decreases by 10 g/L, the risk of dying becomes 1.72 times higher. This relation between Hb value and survival was significant ($P = 0.012$). This risk was higher than that reported by Schellenberg et al. (1999) for hospitalized anemic children <5 y of age in Tanzania who were admitted with Hb <80 g/L (a 10 g/L decrease was associated with 1.3-fold increase in the estimated OR for mortality, 95% CI: 1.04–1.6, $P < 0.02$). A number of interplaying factors must be

FIGURE 1 Case fatality rates in severely anemic children in 10 studies reporting transfusion frequency. $R^2 = 3.4\%$; $P = 0.589$. CI, confidence interval.

controlled for in this model (e.g., low birth weight or anthropometric indexes), but the sample size was small.

Survival rates of severely anemic children (Hb <50 g/L) after admission to hospital have been reported in Kenya by Lackritz et al. (1992) and in the Gambia by Bojang et al (1997). In Kenya, 20.0% (158 of 768) of children died in the first 24 h, although 51.0% received transfusion and 7.3% (37/506) died in the next 24 h, 46.8% of whom received transfusion. In the Gambia, Zucker et al. (1996) reported survival after discharge of children admitted to hospital in Kenya with severe anemia. Severely anemic children (Hb <50 g/L) had higher mortality at both 1 and 2 mo postdischarge than did children who were not severely anemic (1 mo: 14.5 vs. 8.6%; 2 mo: 18.8 vs. 11.3%). In the Malawian community cohort, of the infants who died, there was a higher risk of dying within 1–3 wk if the Hb was < 80 g/L.
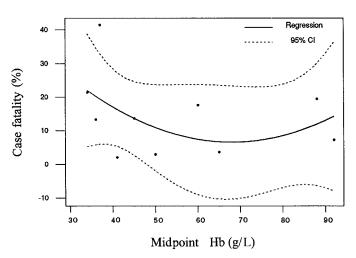
In communities in which α-thalassemia is frequent, homozygous children, who have slightly lower Hb levels than normal, have been observed to have significantly reduced risk of hospital admission with severe malaria (OR: 0.4, 95% CI: 0.22–0.74) and also of admission with nonmalaria infections

(OR: 0.36; 95% CI: 0.22–0.60), which may be an indirect effect of protection against malaria (Allen 1997, Oppenheimer et al. 1987). In such populations, anemia may be observed to decrease morbidity and mortality. This may be the explanation for the observation of Oppenheimer et al. (1986) in Papua New Guinea that birth Hb correlated positively in infants with risk of subsequent hospital admission.

Survival of untreated children with thalassemia major hemoglobinopathies followed in Ferrara in the 1950s showed 20% survival at 3 y (WHO 1982). Usually the homozygous or compound heterozygous state for β-thalassemia causes transfusion-dependent anemia from early life, although some patients run a milder course.
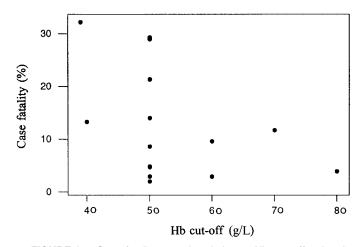
Cause-specific anemia and child mortality

Anemic children in Nigeria come from families with high infant and child mortality (Fleming and Werblinska 1982). In detailed investigations by these authors of 59 children with hematocrit <0.30, the cause was always multiple, associated with viral or bacterial infections, malaria, sideropenia, folate deficiency, hypoproteinemia and sickle cell disease. Zucker et al. (1996) reported primary causation for severely anemic (Hb <50 g/L) hospitalized children in Western Kenya in relation to mortality (**Table 6**). This information has been used to obtain estimates of days of life lost through death for each of these primary diagnostic categories for severe anemia (Ghana Health Assessment Team 1981). Specific case definitions for clinical syndromes were assigned, but some misclassification may have occurred (e.g., no severe anemia was reported in any case of measles).

Average age of onset in affected children was assumed to be 1 y and the expectation of life was assumed to be 53 y (Fleming and Werblinska 1982). The years of healthy life lost per 1000 population per year is calculated as the case fatality rate × the annual incidence of severe anemia × 53. The annual incidence of severe anemia per 1000 live births is calculated as the annual incidence of death due to anemia/the case fatality rate and the annual incidence of deaths due to severe anemia is the proportion of child deaths attributed to severe anemia × the mortality rate for children < 5 y old. The latter is taken as 90 per 1000 live births for Kenya (United Nations Children's Fund 1999).

Table 6 shows the years of life lost because of severe anemia.

FIGURE 2 Case fatality rates and midpoint hemoglobin (Hb) values in anemic children. $Y = 68.4 - 18.2X + 1.34X^2$; $R^2 = 19.6\%$; $P = 0.316$. CI, confidence interval.

FIGURE 3 Case fatality rates in relation to Hb cut-off points in anemic children. At Hb <50 g/L, there are nine plots, two of which overlap and are hidden.

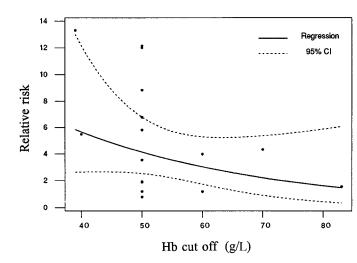## TABLE 5

Relative risk of mortality by severity of anemia[1]

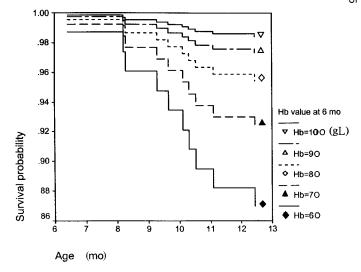| Hb cut-off	Deaths (sample size)	Relative risk A[2] (95% CI)	Relative risk B[2] (95% CI)	Reference
g/L	*n*			
<50	86 (293)	1.5 (1.2–1.9)	12.1 (8.2–18)	Zucker et al. 1996
>50	179 (930)	1.0 (referent)	—	
<70	259 (2471)	5.2 (4.3–6.2)	4.3 (3.0–6.3)	Commey and DeKyem 1995
>70	187 (9182)	1.0 (referent)	—	
<50	8 (175)	1.6 (0.8–3.3)	1.9 (0.9–4.1)	Schellenberg et al. 1999
<80	36 (962)	1.6 (1.0–2.5)	1.6 (1.0–2.5)	
>83	28 (1054)	1.0 (referent)	—	
<50	3 (103)	0.8 (0.2–2.6)	1.2 (0.4–3.9)	Allen et al. 1996
>50	14 (375)	1.0 (referent)		
<50	24 (280)	1.8 (1.2–2.7)	3.5 (2.1–5.8)	Newton et al. 1997
>50	100 (2060)	1.0 (referent)	—	
<39	56 (174)	3.6 (2.8–4.6)	13.3 (8.8–20)	Lackritz et al. 1992
<50	89 (416)	2.6 (2.0–3.3)	8.9 (6.0–13)	
>50	136 (1635)	1.0 (referent)	—	
<50	88 (303)	1.5 (1.1–2.0)	12.0 (8.1–18)	Lackritz et al. 1997
>50	59 (303)	1.0 (referent)	—	
<50	57 (405)	—	5.8 (3.8–8.9)	Slutsker et al. 1994
<50	84 (512)	—	6.8 (4.5–10.2)	Slutsker et al. 1994
<50	15 (320)	—	1.9 (1.1–3.6)	Marsh et al. 1995
<40	23 (173)	—	5.5 (3.3–9.2)	Bojang et al. 1997
<60	101 (1050)	—	4.0 (2.7–5.9)	Brewster and Greenwood 1993
<60	3 (105)	—	1.2 (0.4–3.8)	Holzer et al. 1993
<50	2 (100)	—	0.8 (0.2–3.1)	Van Hombergh et al. 1996

[1] Hb, hemoglobin; CI, confidence interval.
[2] A: Own referent group with Hb between 50 and 80 g/L; B: Referent group from Schellenberg et al. 1999; (Hb >8.3 g/L).

from specific causes estimated with this method and using the published data of Zucker et al. (1996) from Kenya. Malaria and sepsis are the most important contributors. Symptomatic anemia contributes a substantial burden, and this group probably includes children with sickle cell disease. It is difficult to partition iron-deficiency anemia among these diagnoses because it is likely to affect several if not all of these etiological groups. Malnutrition is not a major contributor to death from severe anemia.

To attribute more childhood mortality to malarial anemia than iron-deficiency anemia requires evidence that these two diagnoses could be distinguished correctly. For this reason, these estimates in children from Kenya are limited. They can be compared with data from an iron supplementation and malaria chemoprophylaxis trial for the prevention of infant anemia (Hb <80 g/L) in Tanzania (Menendez et al. 1997). This reported a protective efficacy of 57.3% for malarial anemia and 28.8% for iron-deficiency anemia. The combined intervention had a more significant effect on anemia than did the single intervention. A case fatality of 6.1% was reported for children of all ages from this area with the same level of anemia (<80 g/L) (Schellenberg et al. 1999). **Table 7** shows

FIGURE 4 Relative risk for child mortality in relation to hemoglobin (Hb) cut-off points. Log $Y = 1.30 - 0.137X$; $R^2 = 13.8\%$; $P = 0.156$. CI, confidence interval.

FIGURE 5 Survival curves in Malawian infants in relation to hemoglobin (Hb) values (g/L) at 6 mo.

TABLE 6

Days of life lost due to death from different causes of severe anemia (0–4 y)

Type of severe anemia	Proportion of child deaths attributable to anemia	Case fatality rate	Annual incidence per 1000[1]		Years of life lost
			Death	Illness	
	%	%			
Malaria	11.7	24.6	10.53	42.8	558.1
Bacteremia	8.3	52.6	7.47	14.2	395.9
Malnutrition	0.7	9.5	0.63	6.6	33.4
HIV[2] infection	1.1	50.0	0.99	2.0	52.5
Diarrhea	0.0	0.0	0.0	0.0	0
Pneumonia	2.3	15.0	2.07	13.8	109.7
Febrile illness	2.3	23.0	2.07	9.0	109.7
Symptomatic anemia	3.4	22.0	3.06	13.9	162.2
Measles	0.0	0.0	0.0	0.0	0
Chronic diarrhea	0.7	50.0	0.18	0.36	9.5
Unclassified	1.9	38.5	0.63	1.6	33.4

[1] Years of life lost per 1000 children 0–4 y per year due to death or illness from severe anemia of that cause.

[2] HIV, human immunodeficiency virus.

the infant lives lost because of death from iron deficiency or malarial anemia estimated from this data. These results support the evidence for a strong link between malaria-related anemia and child mortality. The contribution of malaria to iron deficiency is uncertain and research in this area is warranted.

Anemias have been recognized as being associated with protein-energy malnutrition since the earliest classified descriptions, but the pathogenesis of these anemias is complex and involves several variables (Dempster et al. 1995, Watt et al. 1962, Woodruff et al. 1968). Mean Hb values within the range 80–110 g/L are usually reported. Few studies give the proportion of cases with severe anemia, and a recent study from Kenya found that malnutrition (weight for height <2 SD) was not associated with severe anemia in hospitalized children (Lackritz et al. 1997). Risk factors for death have been analyzed mainly in relation to anthropometric assessments, and there appear to be few data on risk of death in severely anemic children with malnutrition. Only one identified report compares Hb levels with survival in a group of 80 children with Kwashiorkor (Tolboom et al. 1986). Fourteen children who died had a mean Hb value of 90 g/L (17.5%), whereas survivors had a mean value of 97 g/L.

Survival of children with anemia from sickle cell disease in developing countries is poorly documented. In Ghana, 3.4% of sickle cell patients in a clinic population were known to have died (Ohene-Frempong and Nkrumah 1994). Table 3 shows that in the emergency room at Korle Bu Teaching Hospital, Ghana, 10.8% of child deaths occurred in children with sickle cell anemia and in Makerere, Uganda, this value was 1.8%. The extent to which iron deficiency contributes to these deaths is unknown. Iron deficiency has been considered uncommon in patients with sickle cell anemia, but reports have documented the coexistence of severe iron deficiency in sickle cell patients (Haddy and Castro 1982, Isah and Fleming 1985, Nkrumah et al. 1984).

The relationship of Hb level to survival has been little

studied in human immunodeficiency virus (HIV)-infected children. In HIV-infected European adults with similar CD4 lymphocytic counts and viral load, the most recent value of Hb was a strong independent prognostic marker for death (Mocroft et al. 1999). Anemia is a frequent complication of HIV infection, and its incidence is associated with progression of HIV disease, prescription of certain chemotherapeutics, black race and female gender. Anemia, particularly anemia that does not resolve, is associated with shorter survival of HIV-infected patients (Sullivan et al. 1998). **Table 8** summarizes estimates of deaths in 1990 and deaths projected (year 2000) from iron-deficiency anemia (all forms) published by Murray and Lopez (1994) in the Global Health Statistics tabulations on the burden of disease. The burden for mortality from iron-deficiency anemia is generally greater in girls, with the highest estimates in China and India, although for boys, deaths attributable to iron-deficiency anemia were highest in Latin America and the Caribbean.

DISCUSSION

Over half of the children in developing countries suffer from anemia, with malaria and iron deficiency being the major etiological factors. In some parts of Africa where malaria infection is sustained throughout the year, severe anemia is responsible for more deaths than cerebral malaria (Snow et al. 1994). Increasingly, the contribution of *Plasmodium falciparum*–associated severe anemia to pediatric mortality is being recognized, even though the causal relationship between malaria parasitemia and Hb concentration is difficult to establish because most children in malaria holoendemic areas are harboring parasites continuously. Nevertheless, this analysis suggests that estimates of mortality due to malarial severe anemia are at least double those for iron-deficiency severe anemia. Standardized prospective hospital-based or community-based multicenter studies are needed in areas with different malaria endemicities to quantify the role of malaria in the causation of anemia, severe anemia and death from malaria.

Mortality is increased in anemic children with Hb values <50 g/L; the prevalence of such values can approach 3–12% in high risk populations. The strength of the causal evidence relating mild-to-moderate anemia to mortality is significantly weaker. It is critical that this question be resolved with the strongest possible research design. Even if the RR is low (<1.5), the high prevalence of this condition in developing

TABLE 7

Infant lives lost due to death from iron deficiency or malarial anemia (Hb <8 g/L)[1,2]

Attributable deaths from anemia	Case fatality rate	Annual incidence anemia per person	Annual mortality per 1000	YLL
	%			
All groups	6.1	0.62	37.8	1772.8
Malaria-related	6.1	0.36	22.0	1031.8
Iron-deficiency anemia–related	6.1	0.18	11.0	515.9

[1] Sources: Estimated from Menendez et al. 1997 and Schellenberg et al. 1999.

[2] YLL, years of life lost; Hb, hemoglobin.

TABLE 8

Deaths attributable to iron deficiency anemia (all forms) in children[1,2]

Region	Deaths 1990				Deaths 2000 projected			
	Number (thousands)		Rate (per 100,000)		Number (thousands)		Rate (per 100,000)	
	0–4 y	5–14 y	0–4 y	5–14 y	0–4 y	5–14 y	0–4 y	5–14 y
EME								
Boys	0	0	0.4	0.2	0	0	0.3	0.1
Girls	0	0	0.4	0.2	0	0	0.2	0.1
FSE								
Boys	0	0	0.5	0.2	0	0	0.4	0.1
Girls	0	0	0.3	0.2	0	0	0.3	0.1
India								
Boys	3	2	4.3	1.5	2	1	2.7	0.7
Girls	3	2	4.5	1.6	1	1	2.7	0.7
China								
Boys	2	1	2.7	0.6	1	0	1.4	0.2
Girls	5	2	8.8	2.0	2	1	4.3	0.7
OAI								
Boys	2	1	4.0	0.8	1	0	2.6	0.4
Girls	2	1	3.8	0.7	1	0	2.4	0.4
SSA								
Boys	2	1	3.6	1.1	2	1	2.6	0.6
Girls	2	1	3.4	1.2	2	1	2.4	0.6
LAC								
Boys	2	1	6.5	1.9	1	1	4.5	1.1
Girls	1	1	5.3	2.3	1	1	3.6	1.3
MEC								
Boys	2	2	4.4	3.2	0	0	0.8	0.4
Girls	2	0	4.4	0.8	1	0	3.1	0.4
World								
Boys	12	5	3.6	0.9	8	3	2.4	0.5
Girls	14	7	4.6	1.2	9	4	2.7	0.6

[1] EME, established market economies; FSE, formerly socialist economies; OAI, other Asia and islands; SSA, sub-Saharan Africa; LAC, Latin American countries; MEC: Middle Eastern crescent.
[2] Source: Murray and Lopez 1994 and 1996.

countries (40–60%) in high risk populations could result in a significant attributable risk of child mortality. However, given the general weakness in the causal evidence relating most iron-deficiency anemia in young children to mortality, it is premature to generate projections regarding population-attributable risk. If mild-to-moderate disease is not an independent risk factor for child mortality, then intervention programs should consider either a test-and-treat approach or have other justifications for universal supplementation.

The burden of this disease assessed as years of life lost is large because mortality is highest in the youngest children. The burden for childhood malarial anemia is greatest in Africa, from where most of the reports originate. Despite the availability of regional estimates from the global burden of disease reports, few clinical data were found on mortality in severely anemic children who were from nonmalarious areas. For example, the inter-American investigation on mortality in childhood did not quantify anemia, although malnutrition was implicated in 56% of all deaths in children 1–4 y (Puffer and Serrano 1973). The paucity of information from nonmalarious locations is a deficiency, and obtaining data from these areas is a priority. The quantitative effect of anemia on child mortality will exhibit proportionate change across different populations with different disease ecology. At times, the etiology of anemia remains unexplained despite careful investigations (Hendrickse and King 1958), and for some key nutrient deficiencies associated with anemia (e.g., folate), no information was identified on mortality risk.

Would improving Hb levels by whatever means lead to reductions in child mortality? Could screening of young children identify those most at risk of death? Further research is required to answer these questions, but evidence in this analysis would suggest that both approaches might be fruitful. Primary prevention of iron-deficiency anemia and malaria in young children could have substantive effects on reducing child mortality from severe anemia.

ACKNOWLEDGMENTS

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DISCUSSION

Participants: Premji, Tielsch, Stoltzfus, Brabin, Pelletier, Lynch, Oppenheimer, Sazawal, Schultink, Levin

Dr. Premji: The sociocultural factor has not really been mentioned in these discussions, and I would like to comment as a practicing physician in this area, especially the East African Coast. We see a lot of severely anemic children being brought to the hospital and eventually they die. Then you start talking to the mother and it comes out quite vividly that 7 d back they had something known as traditional surgery, the uvulectomy. This actually precipitates acute hemorrhage. This is also a major problem and a cause of mortality.

In Tanzania, we have something known as the National Health Management Information System, which was started about 4 y back. It is collecting data from four health facilities in Tanzania. Anemia here is the second leading cause of hospital-based deaths. Number one is malaria. All other anemias are second, at 17.8% of deaths. It is really difficult here to say whether these are iron-deficiency anemia or other nutritional anemias. So, definitely as a public health issue, anemia in a malaria endemic area is a big, big problem.

An additional point that was discussed yesterday, which Brabin found in data from Malawi, is that in the younger age group more males are affected. In the higher age group, more females are dying than males. I have not worked out the concept yet, because as a parasitologist I know that in the younger age group, mosquitoes do not have any sex bias. They equally bite the female and male children. I think these are the first few reports that might be coming out that there is a sex issue.

Dr. Tielsch: I am going to comment on just a few of the traditional epidemiological criteria for causal inference that are most appropriate to this situation. Regarding the strength of the association, the evidence that Brabin presented and the clinical experience in general are strong for severe anemia. There is not much point in arguing about that. As he points out quite rightfully in his paper, much less so for moderate-to-severe anemia. In fact, we are really in a situation where it is hard to find any evidence at all that there is an association with mortality.

Another criterion is replicability. For a cut-off level of <50 g/L, the variation went from 3% case fatality all the way to 35% case fatality. That would not fit the epidemiologist's criterion for replicability. That kind of variation is just enormous.

Biological plausibility is very strong for severe anemia. The critical question is related to mild-to-moderate anemia, especially that caused by iron deficiency, because this is where most of the pool of anemia exists.

In terms of responsiveness to interventions, we do not have any data. I think this is a clear opening for trials to be done in this area. The only way we are going to get responsiveness information is to do some trials. If we did trials that had severe anemia as the outcome instead of mortality as the outcome, I would probably be happy, because I am convinced that severe anemia is a bad thing. You do not want kids to have severe anemia, so that might be a reasonable surrogate.

What about alternative explanations? Almost all these data are from hospital-based studies in incredibly resource-poor settings, where access to care is a huge factor and where thresholds and criteria for hospital admission are going to vary dramatically by time and between institutions. Those kinds of situations make it extremely difficult to disentangle selection bias from true effects of those particular clinical conditions.

My conclusion is that there is strong evidence for a causal association of severe anemia and mortality, especially in malaria endemic areas. Little evidence supports a causal association with mild-to-moderate anemia and mortality, nor for iron-deficiency anemia without malaria, because we have almost no data in that regard. Given the high prevalence of mild-to-moderate anemia, it is critical to know that this increases mortality in areas both with and without malaria.

Dr. Stoltzfus: The relationship to respiratory infection is potentially important. In Siaya, Kenya, mortality rates in hospital went up when hemoglobin levels were below 50 g/L, but that effect was hugely modified by the presence of respiratory illness in the children. Severe anemia and respiratory illness is a very deadly combination for a child to have. This was also apparent in the data that you showed from Kilifi, Kenya. Now, those were malaria-related deaths, but if you have a simple severe anemia as opposed to severe anemia with respiratory distress, the difference in case fatality rates in that hospital was over 10-fold. It also appears in U. K. adult surgical data. If you have severe anemia and cardiovascular disease, it seems like the combination of the low hemoglobin in the blood and a secondary factor that is affecting oxygen delivery, such as poor respiratory function, is a particularly bad combination. It makes me think about India and other places where you do not have malaria but you have lots of children dying from respiratory-related illness. Can we get data from those places to look at the combined effects of anemia and respiratory illness on mortality?

Dr. Tielsch: I guess the other question even before that is: Is this respiratory disease that we see in these malaria hyperendemic areas just another indication of the severity of the malaria?

Dr. Brabin: It can be answered because it has been studied. Some of the children do have malaria. However, as a predictor of outcome, the respiratory distress is closely related to metabolic acidosis rather than pneumonia.

Dr. Sazawal: At least in nonmalarious areas, one of the strong predictors of pneumonia mortality is oxygen saturation. In a community setting, if you did oxygen saturation assessment on children presenting with pneumonia to an outpatient clinic, it strongly correlates with outcome of the pneumonia episode. I assume on a theoretical basis that in anemic children, given the same degree of the insult, whether it is because of pneumonia or whether it is because of bronchitis, it is going to lead to a higher and higher oxygen saturation problem. Theoretically you could predict it, but there are no direct data.

Dr. Pelletier: Yesterday, Brabin, we listened to your methods and came to the conclusion that most of the anemia among women was due to iron-deficiency anemia. In your paper today you are suggesting that it is the reverse. In Africa, one of the things you hear commonly is that malaria is the great leveler, that it strikes without regard to socioeconomic status. Based on the data you presented today, weak as the data are, we are assuming no relationship, except with severe anemia. That is even though Beard said clearly yesterday that experimental data suggest that there is an increased risk of infection during iron deficiency, although a small number of reports indicate otherwise. He encourages caution in the interpretation of many studies, as the confounding issues of poverty, generalized malnutrition, and multimicronutrient deficiencies are often present in those studies. He is talking about iron deficiency and, presumably, if severe enough, iron-deficiency anemia. If all of that is true, if there is an effect of iron deficiency and all these confounding factors that move in the same direction, we should be seeing strong effects on child mortality from poverty, other micronutrients and iron itself. We are not seeing it. It is consistent with what you have seen

in this paper, that maybe malaria is a major cause of anemia among children and it is the great leveler.

Dr. Tielsch: I would not infer that at all. These are all hospital-based data from Africa, basically. You have to be really sick to get admitted to a resource-poor hospital. That is expressed well by the case fatality rates. Some of those case fatality rates are astounding.

Dr. Brabin: I think we look at average data. If you look at all patients and children who are not as sick, malaria is still the major cause of anemia in young children.

Dr. Stoltzfus: Clara Menendez's study in Ifikara, Tanzania, has the best data we have on severe anemia in infancy. With malaria chemoprophylaxis, the incidence of severe anemia was reduced about 60% and with the iron supplementation it was 30%. She infers that those proportions are attributable to iron and malaria and the malaria portion is bigger.

What makes me uncomfortable with that inference is that her iron supplementation intervention was administered from 2 to 6 mo of age. Most of the severe anemia happened between 6 and 12 mo of age. So, I am not convinced that giving those children low-dose iron supplements from 2 to 6 mo of age eliminated iron deficiency in the second half of infancy. Obviously, her intervention pumped up their stores by 6 mo and decreased greatly the amount of iron deficiency, but 28% is probably an underestimate. It is inaccurate to infer that that is the exact amount attributable to iron deficiency in all of infancy. She was not giving iron supplements during the most vulnerable period from a nutritional standpoint, when the children would be the most iron deficient. My point is only that even in a very high endemic part of Africa, the contribution of iron deficiency is fairly substantial to severe anemia.

Dr. Lynch: I agree with you entirely. It is important to remember that the young infant is dependent on a daily iron supply and is not able to build up a big store because of the physiological fact that the body uses the store first and then it pumps up the absorption once the store is gone. I think your inference is very likely.

Dr. Oppenheimer: You cannot completely separate malaria from iron deficiency when you are looking at hemoglobin as the outcome. In our study of iron dextran–supplemented infants in Papua New Guinea, although there was a mean increase in hemoglobin in the intervention group, there was also an increase in severe anemia in the intervention group. Those infants in the iron intervention group who had a positive malaria blood slide had a much lower mean hemoglobin, 70 g/L. For the placebo group, if they had a positive blood slide, their mean hemoglobin, I think, was 85 g/L. Although there was an overall improvement in hematological status measured crudely by hemoglobin, if you are looking at the high-risk anemia cases, there are more of those in the intervention group.

Dr. Stoltzfus: That was not true in Menendez's trial and it was not true in the trial in Zanzibar that we completed that is still unpublished.

Dr. Oppenheimer: I do not think that should always be the case, but you have to look for that interaction. You cannot automatically separate the causes of anemia when you have got iron in there—you have to look at the interactions.

Dr. Stoltzfus: Right, I agree.

Dr. Premji: Another observation that I often make but cannot explain: you have a child who comes to the hospital with, for example, a hemoglobin of 80–90 g/L, which is not bad in our settings. The child has high fever, the blood slide is positive. You may decide to hospitalize this child, maybe for hyperpyrexia, something of that sort. Within 6–12 h, the hemoglobin drops down drastically, and you may lose this child. This is the real scenario. It happens quite often. An acute drop of hemoglobin. Now, that might not be related to the iron stores of this child, but we do not know exactly what is happening. There are quite a number of those and I do not know how you would put that as far as mortality is concerned. Is it due to malaria? Is it due to anemia, an acute drop in hemoglobin?

Dr. Pelletier: If the child survives, what happens to the hemoglobin in the next few days?

Dr. Premji: You give supplements.

Dr. Pelletier: Do you know the normal course?

Dr. Premji: In this case, you have to give a blood transfusion. You may save the child and then you start supplementation. It is a difficult question.

Dr. Lynch: Do they have hemoglobinuria?

Dr. Premji: Some do, but it will still be microscopic, not macroscopic.

Dr. Brabin: I know exactly what you mean. I think some of it may be septicemia. You have to try to make a clinical diagnosis. Some cases cannot be classified.

Dr. Lynch: To go back to the human immunodeficiency (HIV) question, we should all think very carefully about how we look at those intervention trials for HIV and be very careful that we are looking at trials where the iron is being given for iron deficiency, as far as that can be established. Otherwise there is the huge risk of quickly building up a body of data that says iron is bad for HIV anemia. In general, HIV anemia is not going to be iron deficiency—in Western countries anyway. I am not sure about Africa.

Dr. Lynch: In an area like Malawi, where 6–10% of children have HIV, there is a substantial attributable component of anemia due to HIV. These children are relatively reasonably clinically well.

Dr. Brabin: They are not iron deficient, are they?

Dr. Lynch: I do not know. They have a low hemoglobin. It really becomes a crucial issue. If it were true that iron exacerbates HIV infection, it would be the end of iron supplementation, which is why we cannot ignore it.

Dr. Stoltzfus: There is not a lot of purpose in discussing it at this meeting, because the evidence is so scanty. Our discussion right now is focused on malaria. When we talk about sub-Saharan Africa, we are talking about iron deficiency and malaria as competing causes. If we gathered again in 5 y, it could be iron deficiency and HIV and how to disentangle them. It also has implications for our problem definition and surveillance of the problem. As HIV makes its way through the African continent, prevalence of anemia is going to become a worse and worse indicator for surveillance and monitoring and setting global goals for iron deficiency. All evidence is that the prevalence of anemia is going to go up.

Dr. Tielsch: Yesterday it was said that we should look at the full natural course of reproductive outcomes before we make decisions about whether iron supplementation is beneficial. You need to apply the same thinking to the natural history of HIV. If iron is at all associated with the underlying natural history—that is, the progression from infection to clinical manifestation and then from manifestation to death—you really need to understand that full course as well and not just what happens just in one particular scenario. HIV-positive people with iron deficiency may exhibit their anemia very late in the course of their HIV disease, and they are much more ready to die than people who had expressed their clinical symptomatology earlier. I think it is important to have the full picture in mind. The vitamin A story reminds me of that, because the vitamin A story is clearly involved in that whole natural history process as well.

Dr. Lynch: I think that is actually a very important point. The effect of iron on HIV may actually be quite different at different times. It is not necessarily all the same throughout the disease.

Dr. Pelletier: Maybe this is stating the obvious, but this whole discussion brings me back to Stoltzfus's introductory presentation in which a projection showed that perhaps 80% of the world's population is iron deficient in one form or another or with one manifestation or another. What I am taking away from this discussion is that, at least Africa and probably other malarial areas, we actually do not know the prevalence of iron deficiency, in large part because we do not have adequate measures and there are so many different causes of anemia, as measured through hemoglobin. Maybe I am a slow learner, but that is kind of an astounding conclusion, and I would like somebody to correct me if I am getting it wrong. So, we go from 80% to a big question mark.

Dr. Lynch: It is not quite as bad as that. There is reason to believe—and maybe not absolute evidence, certainly not for the individual—that you can select certain groups in whom iron deficiency is going to be a big component. You could identify some age groups, population groups, and issues—hookworm obviously is going to be one—where iron deficiency is going to be highly prevalent. To make a blanket statement about all of Africa is probably wrong. Certainly in southern Africa there is reason to believe that iron deficiency is actually quite uncommon, maybe because of iron pots.

Dr. Sazawal: It is not coming from 80% to zero. In the Menendez paper, 28% is on the table. Given the data, it is safe to conclude that at least that part is iron deficiency.

Dr. Brabin: Also, that is with an influence of very low hookworm infection in infants, whereas hookworm infection rises dramatically with age. So, that is a kind of common denominator and prevalence of iron deficiency anaemia may subsequently rise further with increasing age where hookworm is common. Hemoglobin <80 g/L was the outcome for that study.

Dr. Schultink: You know, iron was the last big micronutrient where we still thought we had a good estimate. For iodine, we had an estimate for goiters, but we do not even start thinking about the real magnitude of the problem of iodine deficiency. Still, that does not prevent us from doing something about it. I think that for programmers there is a plus here: the target in terms of worldwide anemia. Is it the iron-attributable anemia? If so, the target is smaller and we need to recognize where that target is. Then if we can persuade the programmers to focus their efforts on the iron-deficient segments, if we can identify them, we can certainly stop wasting a lot of time on treating the part of the target that is not going to change.

Dr. Levin: Most of these studies are hospital based or observations from clinics. What is the magnitude of the problem outside the hospital. Getting back to programmatic issues, how do you address that?

Dr. Stoltzfus: In rural Zanzibar, of children 6–24 mo of age, 30% have hemoglobin <70 g/L. These were children whom we assessed as clinically well. If they were clinically ill, we did not do the health assessment that way that day. So, there is a huge amount out there.

Dr. Sazawal: What is the prevalence of malaria?

Dr. Stoltzfus: Very, very high, very like the Ifikara population that Menendez studied. So, what proportion of that severe anemia is due to iron? I think it is higher than we thought in the past—higher than I thought in the past. At least 28% of it is. Say that 28% is really 40% or 50%. Then you are talking about still, on a community level, a large amount of severe anemia that is attributable to iron deficiency in malaria-endemic sub-Saharan Africa.