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

Iron and Its Relation to Immunity and Infectious Disease[1,2]

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ABSTRACT The continuing unresolved debate over the interaction of iron and infection indicates a need for quantitative review of clinical morbidity outcomes. Iron deficiency is associated with reversible abnormalities of immune function, but it is difficult to demonstrate the severity and relevance of these in observational studies. Iron treatment has been associated with acute exacerbations of infection, in particular, malaria. Oral iron has been associated with increased rates of clinical malaria (5 of 9 studies) and increased morbidity from other infectious disease (4 of 8 studies). In most instances, therapeutic doses of oral iron were used. No studies in malarial regions showed benefits. Knowledge of local prevalence of causes of anemia including iron deficiency, seasonal malarial endemicity, protective hemoglobinopathies and age-specific immunity is essential in planning interventions. A balance must be struck in dose of oral iron and the timing of intervention with respect to age and malaria transmission. Antimalarial intervention is important. No studies of oral iron supplementation clearly show deleterious effects in nonmalarious areas. Milk fortification reduced morbidity due to respiratory disease in two very early studies in nonmalarious regions, but this was not confirmed in three later fortification studies, and better morbidity rates could be achieved by breast-feeding alone. One study in a nonmalarious area of Indonesia showed reduced infectious outcome after oral iron supplementation of anemic schoolchildren. No systematic studies report oral iron supplementation and infectious morbidity in breast-fed infants in nonmalarious regions. J. Nutr. 131: 616S–635S, 2001.

KEY WORDS: • *iron* • *infection* • *malaria* • *morbidity* • *clinical trial*

Iron deficiency is the most common micronutrient deficiency in the world, especially in the tropics. Prevention of iron deficiency is perceived by health workers as a desirable worldwide goal, preferably provision of iron by the oral route, including fortification of milk and other foodstuffs, although parenteral administration is still used in certain circumstances (Oppenheimer and Hendrickse 1983). However, this dream of universal freedom from an easily preventable disorder has been stalled somewhat since the 1980s.

Although this failure may be mainly one of implementation, one often-mentioned contribution to the problem is the unresolved concern as to the interaction among iron status, iron supplementation and susceptibility to infection (Dhur et al. 1989, Farthing 1989, Hershko et al. 1988, Hershko 1993, Oppenheimer and Hendrickse 1983, Oppenheimer 1994 and 1998, Scrimshaw and San Giovanni 1997). This difficult subject has been polarized by partisan claims either that iron deficiency always helps (the so-called nutritional immunity hypothesis [Kochan 1973, Weinberg 1978]) or always hinders defenses against infection.

The early prospective intervention studies conducted in deprived populations of temperate, developed countries tended to support the value of iron supplements in reducing rates of respiratory infections in infants (Andelman and Sered 1966, Cantwell 1972, MacKay 1928). This rosy picture was not sustained with intervention studies published from the late 1970s on. Side effects of treatment, particularly with parenteral iron, were one problem, and later reports from the tropics seemed to indicate a deleterious effect on susceptibility to both malaria and respiratory infections, thus emphasizing the fact, already known from animal studies, that different organisms interact differently with iron in their hosts.

The malaria issue has dominated the picture since the 1970s, and few significant studies evaluating systematic iron supplementation and infectious morbidity in nonmalarious areas were published in the 1980s. The controversy has been compounded by the lack of adequate control in earlier published prospective clinical intervention studies and the practical impossibility of conducting adequately controlled nonintervention (i.e., observational) studies in iron-deficient humans. Even laboratory measures of iron deficiency are grossly confounded by the immediate presence of infection (Oppenheimer and Hendrickse 1983).

The result has been that although experimental iron deficiency in animals and in vitro functional effects on immunity

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in humans have been usefully studied for decades, numerous clinical reviews still seem unable to make clear quantitative statements about how important iron deficiency is to human infectious morbidity. Although more controlled studies must be done, there is still useful information to be gleaned from the literature as long as the older intervention studies are not all rejected out of hand because of design faults.

Criteria for inclusion of studies and evaluation of a relationship

This review is directed primarily at the clinical and epidemiological evidence for a causal relationship between iron deficiency and infectious morbidity as shown by controlled intervention studies of iron supplementation. As has been stated, clinical studies in countries with endemic malaria tend to have produced effects opposite to those in nonmalarious climes; thus, results are discussed and summarized in tabular form separately for these two situations.

A preexisting database of reports (Oppenheimer 1994 and 1998) was supplemented with the use of the following: *1*) MEDLINE search, using combinations of the keyword "iron" crossed separately with "supplement," "infection," "trial" and "immunity"; the results were hand-searched; *2*) personal communications with workers involved in existing trials; and *3*) search of the Cochrane Controlled Trials Register. All studies mentioning infectious outcome were reviewed, but only controlled studies with quantified clinical infectious morbidity are discussed here. The only further exclusions from the latter were studies in which another micronutrient apart from iron was combined with iron as an intervention but not given to the placebo group.

Design, participant selection and multiple outcomes of these studies were so qualitatively heterogeneous that meta-analysis may have limited meaning, and this review concentrates on the possible ecological reasons for the different outcomes. To obtain some consistency in tabular and graphic presentation of outcomes, however, odds ratios (OR)[3] [with a fixed-effects model and 95% confidence intervals (CI)—RevMan 4.0.4 (Cochrane Collaboration)] based on the dichotomous contingency "no morbid event vs. one or more events" *per individual*, over a stated time period—are given, where published data allow. In some studies, this contingency is not available because total morbid events rather than individuals were given as the numerator. If OR could not be calculated from available information, the actual published rates, relative risks or both are quoted in tables only and omitted from OR plots. In several studies, follow-up wastage was high, thus introducing potential systematic bias in rates. For these studies, therefore, realistic average surveillance denominators are estimated from available information. Only clinically relevant morbidity outcomes are cited. Functional laboratory immunological outcomes and malarial parasite prevalence rates have been dealt with elsewhere (Dhur et al. 1989, Farthing 1989, Hershko 1993, Oppenheimer and Hendrickse 1983, Oppenheimer 1994 and 1998, Scrimshaw and San Giovanni 1997, Shankar et al. 2000).

During the review of studies, subsidiary questions were addressed, such as whether potential causal effects are graded and what, if any, are the laboratory measurements that predict the morbidity outcome most closely. In the absence of clear answers to the primary questions in humans, such issues can only be flagged, not answered.

Before the discussion of interventions, an overview will be made of the in vitro evidence for functional immunological effects of iron deficiency and supplementation along with evidence for how this interfaces with specific infections. This is supplemented by a review of nonintervention iron deficiency and morbidity reports.

In vitro studies of iron deficiency and functional immunity

Two component systems of active immunity—humoral and cell-mediated immunity—have been studied extensively, mainly in vitro, in relation to iron deficiency in both humans and animals. Little evidence exists for systematic major humoral deficiencies in iron-deficient humans, and although specific defects in cell-mediated immunity have been well described and reviewed, even in latent iron deficiency, note that such minor functional changes cannot be compared with the devastating effects of the well-defined immunodeficiency syndromes (Dhur et al. 1989, Farthing 1989, Hershko 1993, Oppenheimer and Hendrickse 1983, Scrimshaw and San Giovanni 1997). Little information is available on whether effects are graded by degree of iron deficiency; they may even be present before hemoglobin is lowered. Intensively studied deleterious effects of iron deficiency on cellular defenses that are reversible with iron therapy include the following: *1*) Reduced polymorph neutrophil function with decreased myeloperoxidase activity and nitro blue toluene reduction reversed by iron administration. Intracellular bacteriocidal activity has been reported as impaired, but not all studies give consistent results (Dhur et al. 1989, Farthing 1989, Hershko 1993, Oppenheimer and Hendrickse 1983, Scrimshaw and San Giovanni 1997). *2*) Depression of T-lymphocyte numbers with thymic atrophy, and most but not all studies concur (Dhur et al. 1989, Farthing 1989, Hershko 1993, Oppenheimer and Hendrickse 1983, Scrimshaw and San Giovanni 1997). *3*) Defective T lymphocyte–induced proliferative response, with slightly more reports showing an effect than not showing an effect (Farthing 1989). *4*) Impaired natural killer cell activity (Dhur et al. 1989). 5) Impaired interleukin-2 production by lymphocytes (Galan et al.1992). 6) Reduced production of macrophage migration inhibition factor (Dhur et al. 1989, Farthing 1989). *7*) Reversible impairment of delayed cutaneous hypersensitivity, including tuberculin reactivity; in general there is agreement for this finding (Farthing 1989, Moraes-de-Souza et al. 1984).

Proteins in iron metabolism. The third set of defense systems that are uniquely associated with iron metabolism are cellular and extracellular iron-binding proteins (transferrins and lactoferrin). These inhibit bacterial growth by withdrawing iron.

Almost 30 years ago, Bullen et al. (1972) showed that the bacteriostatic action of human milk is abolished by in vitro addition of iron. In this context, Murray et al. (1980) showed an increase in *Entamoeba histolytica* infection in nomads who drank cow's milk during supplementation with oral iron. This was not seen in the nonrandomized control group or in those receiving parenteral iron. They related the effect to saturation of the cow's milk lactoferrin by oral iron.

Cow's milk formulas contain no active lactoferrin, and therefore iron fortification in theory should not compromise artificially fed infants. However, there has been debate about the advisability of giving oral iron to breast-fed infants. One thing that is clear is that formula milk, with or without iron, can carry a higher risk of infectious morbidity than breast-

[3] Abbreviations: CI, confidence interval; DFO, desferrioxamine; HIV, human immunodeficiency virus; NRAMP, natural resistance–associated macrophage proteins; OR, odds ratio.

feeding in deprived communities (Heresi et al. 1995). Lonnerdal et al. (1980) pointed out that because the bulk of the iron in breast milk is not attached to lactoferrin and yet is highly bioavailable for the infant, an alternative method of oral iron supplementation for infants might be to supplement lactating mothers.

"Nutritional immunity." The growth of a variety of bacteria and fungi are inhibited in vitro by transferrin and lactoferrin (Kochan 1973, Weinberg 1978). The thesis of nutritional immunity elaborates this well-known defense mechanism by arguing that "further lowering of the saturation of iron in transferrin or lactoferrin further enhances immunity." In practice, however, this thesis appears to have been overstated for extracellular microbial pathogens (Oppenheimer and Hendrickse 1983). Virulent invasive pathogens usually have their own powerful siderophores that are quite capable of removing iron from transferrin, whereas less virulent opportunistic infections such as *Escherichia coli* are equally inhibited from growing in plasma over a wide range of transferrin saturations, corresponding to different physiological states of iron balance (Oppenheimer and Hendrickse 1983). In other words, iron-deficient individuals may not be especially protected from such opportunistic infections. Equally, lowered transferrin saturation does not affect the virulence of disseminating organisms with high iron avidity (Oppenheimer and Hendrickse 1983).

One group of microorganisms with an iron requirement in a special situation in relation to iron availability comprises the erythrocytic forms of malaria. Although inside cells with the highest iron content in the vertebrate body, plasmodia are apparently unable to use this source effectively nor do they seem able to extract transferrin-bound iron from the plasma surrounding the red cells. Much work over the past 15 years has centered around the observation that iron chelators can inhibit malarial growth in vitro as well as in vivo (Hershko et al. 1988). A recent in vitro study appears to confirm the longstanding theory that a small labile pool of iron in red cells (which may be crucially smaller in people with iron deficiency) provides the iron the parasite requires (Loyevsky et al. 1999). This may provide one mechanism that underlies clinical observations suggesting that iron deficiency may protect from malaria.

The qualitative differences between iron-pathogen interactions in the extracellular compartment and those that are intracellular have recently been refocused by study of the natural resistance associated macrophage proteins (NRAMP 1, 2) and the role of NRAMP 1 in resistance to infection by actively removing intracellular iron. NRAMP 1 targets the membrane of microbe-containing phagosomes in macrophages and monocytes. Allelic variants of NRAMP 1 have recently been found to be associated with susceptibility to tuberculosis and leprosy in humans (Canonne-Hergaux et al. 1999). This finding may be relevant to the differential susceptibility of people to infection by intracellular pathogens according to their iron status.

To summarize in vitro evidence, iron deficiency depresses certain aspects of cell-mediated immunity, including lymphocyte, neutrophil and macrophage function; humoral immunity is unaffected and the significance of hypoferremia (as opposed to normal transferrin saturation) on growth of microorganisms is uncertain. In contrast, one group of intracellular organisms, *Plasmodia*, may have a specific disadvantage in iron deficiency. Because there are conflicting effects of deficiency and treatment on defense systems, it becomes more important to study the situation in vivo.

Observational studies on iron deficiency and infectious morbidity

Iron deficiency and its effect on infection are difficult to study in humans using observational or noninterventional means. This is because iron deficiency is part of a cluster of nutrient and social deprivations, ultimately resulting from poverty, that are inevitably interrelated. There is also an ethical problem with prolonged study of people known to be iron deficient while withholding treatment. Therefore, we will start with a brief overview of the effects of iron deficiency (and changes after supplementation) on infectious morbidity in animals. These results, although unable to answer the main questions, may give pointers as to what to look for in clinical and epidemiological studies.

In vivo studies in iron-deficient animals. In view of the potential problems of confounding when relating iron deficiency to immune status in humans, it is worthwhile looking at the more controlled observations available from animal studies. Experimental studies in laboratory animals uniformly show reversible deleterious effects of iron administration on tests of functional immunity. These may occur even in mild deficiency. Reports of graded effects are contradictory (Dhur et al. 1989, Scrimshaw and San Giovanni 1997). The picture is not clear, however, with experimental studies of effects on morbidity. Experimental studies of infectious challenge and subsequent morbidity in iron-deficient animals have produced conflicting results (Dhur et al. 1989). Hart et al. (1982) using *Proteus mirabilis*–induced pyelonephritis in rats showed differential effects, with severe iron deficiency protecting less than mild deficiency. Baggs and Miller (1973) claimed that severe deficiency enhanced defenses in rats against invasive *Salmonella*, whereas mild deficiency impaired them. Preweaning iron deficiency produced permanent immune defects. Puschmann and Ganzoni (1977) showed increased resistance of iron-deficient mice to invasive *Salmonella typhimurium* infection, whereas Chu et al. (1976) showed an increased mortality of severely iron-deficient rats infected with *Streptococcus pneumoniae* compared with controls. Harvey et al. (1985) showed reduced parasitemias and reduced mortalities in iron-deficient mice infected with *Plasmodium chabaudi*. Perhaps the only partially unifying message to be gained from these studies is that effects are microorganism specific and that iron deficiency may be more likely to protect against intracellular than extracellular pathogens.

Observational studies in iron-deficient humans. Because of problems of control and confounding, few observational clinical studies in iron-deficient humans convincingly relate such deficiency to substantial morbidity due to infections. Some studies have noted anemia in children admitted to hospital for various infections, but these data could not establish causality (Kaplan and Oski 1980, Lovric 1970, Oppenheimer 1980). Higgs and Wells (1973) noted that of 31 patients with chronic mucocutaneous candidiasis, 23 were iron deficient and 9 of 11 improved with oral and parenteral iron therapy alone, with a regression of oral lesions and development of delayed hypersensitivity to *Candida*. There was no control group. In another report, 16 patients with recurrent staphylococcal furunculosis also had nonanemic iron deficiency. Furunculosis resolved after 3–4 wk of iron therapy in all but one patient (Weijmer et al. 1990).

In one prospective study, postoperative complications, in particular, infections after abdominal surgery, were reported to be significantly more common in 228 patients with low preoperative serum ferritin compared with 220 patients with normal ferritin; confounders including hemoglobin levels were

taken into account in the analysis (Harju 1988). Reports from the tropics are difficult to evaluate because of limited ascertainment of the causes of anemia. In an often misquoted study, Masawe et al. (1974) reported fewer bacterial infections in patients admitted with simple iron deficiency anemia than in a control inpatient group with a variety of other causes of anemia (megaloblastic and refractory), but they also reported more frequent malaria in the iron-deficient patients (8 of 16 cases after initiation of therapy). Unfortunately, they did not give details of which patients were receiving oral or parenteral therapy or whether patients had received therapy before admission.

In their report of the effects of iron treatment in Somali nomads, Murray et al. (1978) also noted that nomads entering a feeding camp had no infections if they were iron deficient ($n = 26$) in contrast to a high rate of infection in those with normal iron status (19 of 64). This unblinded study is difficult to assess. In contrast, Snow and colleagues (1991) attempted to determine whether measurement of iron status in 1- to 9-y-old Gambian children before the start of the malaria transmission season could predict malarial experience and morbidity during that season. They did not find a significant correlation between any hematological measures of iron status and subsequent malarial experience in this older age group.

Possible evidence for a protective effect of low iron stores at birth on subsequent malarial morbidity was obtained in a prospective study conducted by the author in Papua New Guinea (described in more detail below) (Oppenheimer et al. 1986a and 1986b). Infants with lower hemoglobin values at birth were less likely to have malaria at field follow-up and less likely to be admitted to hospital during y 1 of life. Because birth hemoglobin is the main iron source during the first year, this association may mean that iron deficiency protects from malaria and other infections. This association may, alternatively, have resulted from the associated protective effect of homozygous single-deletion α-thalassemia, which is present in >50% of that population. Indeed the high prevalence of single-deletion α-thalassemia in many tropical areas may have a confounding effect in many studies of iron, anemia and morbidity because the mutation both causes anemia and protects against malaria and other infections (Oppenheimer et al. 1987). Allen and colleagues (1997) showed in a subsequent case-control study in the same part of New Guinea that people with homozygous α+-thalassemia were much less likely than controls to develop severe malaria (OR 0.40; 95% CI: 0.22–0.74) and to be admitted to hospital for nonmalarial infections (OR 0.36; 95% CI: 0.22–0.60).

In the study of Oppenheimer et al. (1986a), the predictive value of hemoglobin measured at birth was an exception to the generally low predictive value of hematological measures for subsequent morbidity. Measures of iron status such as hemoglobin, transferrin saturation and ferritin taken at birth and at 2 and 6 mo were of no predictive value for subsequent infectious outcome. Changes in both ferritin and transferrin saturation acted more as acute-phase responses to acute infection. Use of hemoglobin as a surrogate for iron status in infectious morbidity studies is thus clearly fraught with potential for confounding. This was clearly demonstrated in the large iron intervention study of Gebreselassie (1996) in Ethiopia (see also below). Pretrial cross-sectional assessment of the cohort showed that anemia was significantly associated with malaria (OR 1.31; 95%CI: 1.03–1.66), acute respiratory infection (OR 1.33; 95% CI: 1.05–1.69) and diarrhea (OR 1.74; 95% CI: 1.28–2.40). However, no relationship was detected between the same morbidity indicators and the more reliable iron measures of mean cell volume and serum ferritin taken at the same time. Whether the lower hemoglobin of the sick children resulted from iron deficiency or was secondary to their infections is therefore not clear.

Confounders in observational studies on iron deficiency. Clearly there are many problems and differences in design between these observational reports on iron deficiency in the tropics that make it difficult to draw useful conclusions. Another major confounding difference is the age of the study respondents, i.e., younger immune-naive infants appear to show an advantage of low iron status, whereas older semi-immune children do not. Other confounders may interact with immediate effects of iron treatment and will be considered next.

Iron intervention does not simply reverse iron deficiency

Much of the confusion and many of the conflicting results of intervention studies stem from confounding factors that may affect immune and iron status of the populations under study. These include age, past immune experience, diet and cooking practice, and common inherited disorders of globin genes, which may, depending on type and zygosity, protect from malaria, lose their protective efficacy during iron supplementation or predispose to iron overload. Temporary overload may also result from treatment, in particular with parenteral iron.

Estimation of the effects of iron treatment on body iron compartments depends on the dose and route of administration and time elapsed since the start of treatment. There is a massive but short-term hyperferremia after parenteral administration of iron that lasts up to 3 wk after intramuscular iron dextran (Will 1968) or 2–3 d after intravenous iron dextran (Kanakakorn et al. 1973). Circulating iron dextran complex may be a source of iron for bacterial growth immediately after injection, and serum bacteriostatic action is lost during this period. This size of effect is not seen with oral iron supplementation in normal doses (Gross 1968), although gut intraluminal iron may be high (Murray et al. 1980). The hyperferremic effect of parenteral iron is a particular danger during the neonatal period, when such therapy is contraindicated in all circumstances (Becroft et al. 1977).

In the 1970s, several poorly controlled studies incriminated iron therapy in acute exacerbations of preexisting or latent infections. In most of these reports, parenteral iron was used. The report of Masawe et al. (1974), which included infections after iron therapy, was already mentioned. Byles and D'Sa (1970), in a poorly controlled study, reported 11 cases of clinical malaria in 917 pregnant women immediately after parenteral iron therapy.

In New Zealand, serious *E. coli* sepsis was reported in the mid-1970s by Barry and Reeve (1977) in 2% of Polynesian neonates who received 250 mg iron dextran at birth (in five daily doses) (**Table 1**). The increase in infections was confined to the week after the last injections and was detected retrospectively with the attendant problem of validity. Neonatal sepsis fell to 0.2% after discontinuation of this practice. A similar finding, also in New Zealand, was made by Farmer and Becroft (1976). In this case it was neonatal *E. coli* meningitis that was specifically higher in those receiving parenteral iron (Table 1; **Fig. 1**). In confirmation of the postulated mechanism, Becroft et al. (1977) showed a marked reduction in the bacteriostatic action of serum of these neonates on *E. coli* in vitro. Despite the obvious methodological problems of these retrospective studies, the evidence for increased *E. coli* sepsis in neonates is strong.

The early neonatal period is, in any case, a bad time to give

TABLE 1

Numerical summary of morbidity outcomes in iron supplementation trials in nonmalarial regions[1]

Study		Numerator #/Denominator		Odds ratio Fe:Pl	95% Confidence intervals	1/OR Pl:Fe	Comments on study design (ranked)	Trial type
		Iron	Placebo					
Cantwell 1972 New Zealand	Pneumonia admissions	5/94	17/144	0.412	0.146–1.205	2.383	PCRS; CA	Parenteral iron 250 mg IM at birth
	Pneumonia + URTI admissions	7/94	30/144	0.306*	0.126–0.741	3.271		
	All infectious admissions	30/94	61/144	0.638	0.471–1.111	1.568		
	Gastroenteritis admissions	1/93	6/138	0.247	0.029–2.085	4.043		
James and Coombes 1960 U.S.A.	Admissions for lower respiratory infections	24/66	23/74	1.267	0.627–2.559	0.789	PCRS; ED; CA; LN	Parenteral iron 250 mg IM on achieving 2 kg weight
	Admissions for diarrheal infections	7/66	5/74	1.637	0.493–5.430	0.611		
	Outpatient visits with lower respiratory infections	20/66	23/74	0.964	0.469–1.980	1.037		
	Outpatient visits with diarrheal infections	9/66	20/74	0.426	0.178–1.017	2.346		
Angeles et al. 1993 Indonesia	Respiratory infections (daily ACD)	4/39	10/37	OR: 0.31	0.09–1.09	3.22	PCRS CA; LN	Oral iron 30 mg/d 2–5 y for 2 mo
	Diarrhea (daily ACD)	2/39	6/37	OR: 0.28	0.05–1.48	3.57		
Mitra et al. 1997 Bangladesh	Infant dysentery (alt daily ACD) Rates/child y (*n*):	5.2 (34)	3.5 (44)	RR: 1.49*	—	0.67	Multiple events per child; PCRS; CA; LN	Oral iron 15 mg/d 2–48 mo: 15 mo
	Infant ALRTI (alt daily ACD) Rates/child y (*n*):	7.5 (32)	6.9 (44)	RR: 1.09	—	0.92		
Javaid et al. 1991 Pakistan	Respiratory infections (weekly ACD)	11/29	24/57	OR: 0.84	0.34–2.10	1.19	PCRS Oral recall; LN	Fortification of cereal 4.5 mg/d
	Diarrhea (weekly ACD)	25/29	50/57	OR: 0.88	0.23–3.27	1.25		
Heresi et al. 1995 Chile	Respiratory tract infections (oral ACD monthly)	1218/458;	1395/509	RR: 0.930	—	1.076	Oral recall; multiple events/child; PCRS	Milk fortification 15 mg/100 g birth
	Gastro-intestinal infections (oral ACD monthly)	485/458	580/509	RR: 0.970	—	1.031		
Power et al. 1991 South Africa	Total recorded infections (oral ACD 3–4 wk)	413/70	397/62	RR: 0.922	—	1.085 0.950	Morbidity: oral recall Multiple events per child; PCRS; LN	Milk fortification 40 vs. 8.3 mg Fe @ 3 mo for 9 mo
	Respiratory tract infections (oral ACD 3–4 wk)	140/70	118/62	RR: 1.053	—			
	Gastro-intestinal infections (oral ACD 3–4 wk)	63/70	68/62	RR: 0.818	—	1.222		
Barry and Reeve 1977 New Zealand	Severe neonatal sepsis	27/1582	3/1098	6.34*	1.872–21.46	0.158	Retrospective in consecutive years	Parenteral iron 250 mg IM: birth
Farmer and Becroft 1976 New Zealand	*Escherichia coli* meningitis in neonates	21/10[4]	3/10[4]	7.0*	2.036–24.06	0.143	Retrospective in consecutive years	Parenteral iron 250 mg IM: birth
Andelman and Sered 1966 U.S.A.	Respiratory infections wk 1–12 of trial (ACD)	1/449	37/417	0.023*	0.003–0.175	43.62	Morbidity: oral recall Unblinded; PCRS; ED	Milk fortification Fe: 10 mg/L milk
	Respiratory infections wk 13–24 of trial (ACD)	32/351	50/331	0.564*	0.355–0.912	1.774		
	Respiratory infections wk 26–36 of trial (ACD)	68/565	62/294	0.512*	0.348–0.753	1.953		
	Respiratory infections wk 37–52 of trial (ACD)	45/321	40/180	0.571*	0.353–0.924	1.752		
	Respiratory infections wk 53–68 of trial (ACD)	60/302	42/146	0.614*	0.385–0.978	1.63		
Mackay 1928 U.K.	Respiratory infections in winter (ACD/PCD)	14/35	98/135	0.252*	0.555–0.114	3.973	Nonrandomized controls: consecutive years Unblinded; CA	Milk fortification ~50–100 mg/d for 1 y age 3 wk–18 mo
	Respiratory infections in summer (ACD/PCD)	9/52	33/100	0.425*	0.992–0.182	2.353		
	Diarrheal infections in winter (ACD/PCD)	6/35	45/135	0.414	1.087–0.157	2.417		
	Diarrheal infections in summer (ACD/PCD)	12/52	29/100	0.734	1.622–0.333	1.362		

[1] OR/RR, odds ratio/relative risk; Fe/Pl, iron/placebo; (#) where OR (95% int.) given, numerator refers to individuals with one or more morbid episodes; URTI, upper respiratory tract infection; IM, intramuscular; ACD/PCD, Active/Passive case detection; (ALRTI) acute lower respiratory tract infection; (*) effect significant at 5% level or less; PCRS, prospective controlled randomized study; CA, clinical assessment; ED, estimated denominators; LN, low/inadequate numbers. Studies are ranked in order of design quality. Design criteria used: bias—adequacy of randomization, control, and blinding and follow-up retention; cohort definition and size; and methods of morbidity reporting.

TABLE 2

Summary of study design of iron supplementation trials in malarial zones with associated infectious morbidity

Study	Country	Trans.[1] intensity	Sample size *n*	Eligibility criteria	Age	Fe dose	Duration of suppl.	Malaria case definition	Study design and morbidity detection (ranked)	Began suppl.	Malaria seasonality[2]
Oppenheimer et al. (1986b)	PNG[3]	Very high	468	None	2 mo	im 150 mg, one time	one injection	Clinical assessment and Pf > 0	PCRS; age cohort; all morbidity: clinical exam; ACD and PCD: HAd and field	Year round	Seasonal, Aug–Jan
Menendez et al. (1997)	Tanzania	Very high	411	PCV > 25%	2 mo	po 2 mg/(kg · d)	16 wk	F > 37.5 and Pf > 0	PCRS; age cohort; only malaria: clinical exam; ACD & PCD had and field	Year round	Perennial, Mar–June, Dec–June
Adam (1996)[4]	Ethiopia	Medium	841	6 < Hb < 11 g/dL	6 mo–7 y	po 3 mg/(kg · d)	12 wk	S	PCRS; all morbidity: clinical exam poststudy; ACD	May	Seasonal, May–Apr June–Sept
Adam (1996)[4]	Ethiopia	Medium	776	Women, 6 < Hb < 12 g/dL	15–49 y	po 60 mg/d	12 wk	S	PCRS; all morbidity: clinical exam poststudy; ACD	July	Seasonal, May–Apr June–Sept
Gebreselassie (1996)[4]	Ethiopia	Medium	500	5 < Hb < 12 g/dL, Pf-	5–14 y	po 60 mg/d	12 wk	F > 37.5 and S	PCRS; malaria only: clinical exam poststudy; ACD; field	Feb	Seasonal, Sept–Nov
Hombergh (1996)	Tanzania	High	100	Mal/para + Hb ≤ 5 g/L	1–30 mo	po 200 mg/d	12 wk	na	PCRS; LN; All morbidity; field ACD and PCD 2, 4, 8 and 12 wk; clinical exam	Recruited: April–June	Seasonal, Apr–June/Oct–Jan
Berger et al. (2000)	Togo	Medium	163	Hb > 8 g/dL	6–36 mo	po 2 mg/(kg · d)	3 mo	>3000 prbc	PCRS; LN; all morbidity ACD/PCD; clinical exam	Wet through dry season	Seasonal
Rice et al. (1998)[4]	Tanzania	High	608	None	6 mo–5 y	po 10 mg/d	52 wk	na	PCRS; weekly field ACD oral recall; nonmedical fieldworker; malaria only	Sept.	Perennial Apr–June
Smith et al. (1989)	Gambia	Medium	213	5–11 g/dL	6 mo–5 y	po 3–6 mg/(kg · d)	12 wk	F > 37.5 and Pf > 0	PCRS; weekly field ACD oral recall; nonmedical fieldworker; malaria only	July	Seasonal, July–Nov
Harvey et al. (1989)	PNG	Very high	318	8 < Hb < 12 g/dL	8–12 y	po 130 mg/d	16 wk	S	PCRS; oral history and school absence; ACD malaria and gastroenteritis	June	Seasonal Aug–Jan
Murray et al. (1978)	Ethiopia	None	138	Hb < 11 g/dL	11–60 y	po 180 mg/d	4 wk	F > 38 and Pf > 0	PCRS; LN unblinded; weekly ACD field; clinical exam	na	None

[1] For malaria seasonality descriptors are seasonal or perennial transmission followed by the rainy season(s). Studies are ranked in order of design. Design criteria used: bias—adequacy of randomization, control, and blinding and follow-up retention; cohort definition and size; and methods of morbidity reporting.

[2] Transmission intensity based on estimated infective bites per year per person: none = 0; low = >0 to <2; medium = 2 to <10; high = 10 to <100; very high = 100+.

[3] Abbreviations: po, per os; im, intramuscular; PNG, Papua New Guinea; na, not available; PCRS, prospective controlled randomized study; ACD and PCD, active and passive case detection; Had, hospital admissions; LN, low or inadequate numbers; F, fever; S, symptoms consistent with malaria e.g., fever and/or headache thought to suggest malaria; Pf, *Plasmodium falciparum*.

[4] Unpublished.

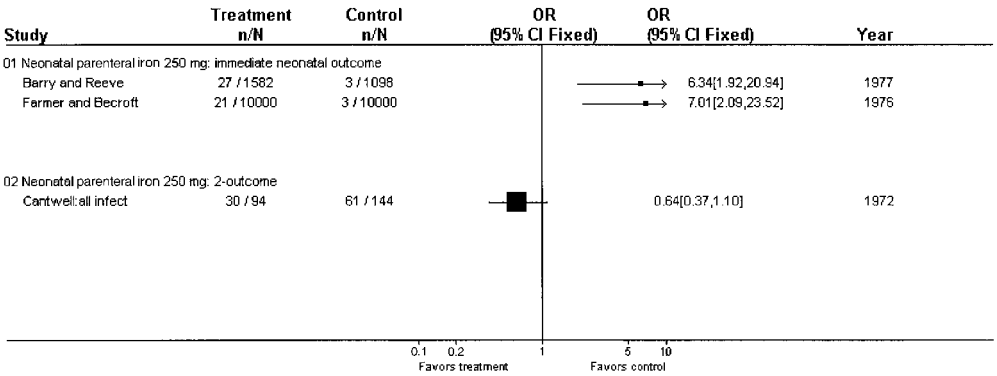

FIGURE 1 Iron trials in nonmalarious regions. Outcome: serious infections (all types). Method of administration: neonatal parenteral iron. Method of morbidity quantification: retrospective passive case detection using historical controls (1: Barry and Reeve 1977, Farmer and Becroft 1976); prospective passive case detection of admissions and in-patients (2: Cantwell 1972). Abbreviations: OR, odds ratio; CI, confidence interval (all figures).

injections of iron. The neonate has a high iron saturation (Saarinen and Siimes 1977) and a vulnerable immune status (Forman and Stiehm 1969, Miller 1969). Farmer (1976), as a follow-up to the initial New Zealand reports, noted that the high incidence of neonatal *E. coli* meningitis associated with iron dextran injection was reduced when no premature infants had received injections at <1 mo of age and there had been more selective administration.

Although most the above immediate adverse effects were associated with parenteral therapy, an important and often-quoted study in the 1970s used oral iron. A family team (Murray et al. 1978) conducted a prospective placebo-controlled randomized trial of 30 d oral iron supplementation in 137 adult Somali nomads with iron-deficiency anemia. Iron treatment increased hemoglobin and transferrin saturation during the study. Although no malaria was noted at the start of the study in either group, 13 clinical attacks of malaria occurred in the iron group ($n = 71$) and only 1 in the control group ($n = 67$) by the end of the trial; these attacks were presumed by the authors to be reactivations (**Table 3**). Fevers were significantly more common in the iron group and eight nomads in the iron group started excreting *Schistosoma* ova in the urine compared with no new cases in the placebo group. The study was single blind, and no follow-up was made after the 30 d of treatment, although the treatment group still had high reticulocyte counts and higher transferrin saturations than the control groups at the end of this period. Documentation of infections was limited to laboratory identification of a pathogen.

Long-term prospective controlled iron intervention studies

In all of the above adverse reports, infections were noted shortly after commencement of iron therapy. It is thus clear that prospective long-term studies are required to separate the early effects of treatment from the effects of steady-state improved iron balance. Only studies with an identified control group (whether double-blind, randomized or otherwise) are reviewed here; a further number had to be excluded for lack of usable quantitative morbidity outcome data (Burman 1972, Chippaux et al. 1991, Fleming et al. 1986, Lawless et al. 1994, Menendez et al. 1995, Nwanyanwu et al. 1996, Salmi et al. 1963, Schneider et al. 1995, Tonkin 1970, van Hensbroek et al. 1995) or because there had been mixed interventions (Bates et al. 1987, Damodaran et al. 1979, Premji et al. 1995). Because it is abundantly clear that the designs and outcomes of the remaining studies in nonmalarious (13 studies) and malarious (11 studies) areas are qualitatively different (e.g., food fortification studies), they will be discussed separately.

Prospective studies in nonmalarious areas. The earliest longitudinal inquiry into the effects of iron supplementation on infection rates was that of Helen MacKay (1928) who reported that infants in London aged 3 wk to 18 mo given dietary supplements of iron had 50% fewer respiratory and gastrointestinal infections than infants not supplemented. Odds ratios estimated from her data showed a significantly reduced risk of respiratory infections associated with iron supplementation. Both method of administration (which included fortified milk) and dosage of iron (~50–100 mg/d) varied among infants; unfortunately, observations on study and control groups were not blinded and, although covering 1 y in each group, were not made in the same year (Table 1; **Fig. 2**).

In a prospective, blank-controlled trial of 250 mg intramuscular iron dextran in premature infants in Texas, James and Coombes (1960) found no significant differences between control and intervention for hospital admissions and outpatient visits for any disease in 171 infants followed for 1 y. Unlike the New Zealand studies, iron was not given at birth but after infants had achieved 2 kg of weight (Table 1; Figs. 2 and **3**).

The largest longitudinal study of iron supplementation was that of Andelman and Sered (1966) in Chicago, in which 1048 infants were randomly assigned to receive formula milk with or without iron fortification (~10 mg elemental Fe/L). Follow-up was for 18 mo. Anemia [hemoglobin (Hb)<100 g/L] occurred in 76% of the control and 9% of the study group. These cases were then unfortunately removed from analysis. No details of methods of morbidity recording were given, and mother's recall apparently was used. Odds ratios calculated from the presented data using estimated denominators show a significantly reduced risk of respiratory infections associated with iron supplementation at each 3-mo follow-up to 68 wk (Table 1; Fig. 2).

Burman (1972) conducted a similar placebo-controlled study using oral colloidal ferric hydroxide (10 mg Fe/d) in Bristol. Again, methodology of morbidity recording was not elaborated and no figures were actually given. No differences in illnesses were noted between the control and study groups, but the small difference in Hb values between the two groups reached significance only in the 2nd y, suggesting a low rate of iron deficiency in any case in the placebo group.

Salmi et al. (1963) reported twice the incidence of infec-

TABLE 3

Numerical tabulation of infectious morbidity outcomes for iron supplementation trials in malarial zones (where recorded)[1]

	Morbidity measure	Number #/Iron	Denom; Placebo	Odds ratio Fe:Plac	(95% confid intervals)	Inverse OR Plac:Fe	Comments
Oppenheimer et al. (1986b)	Clinical malaria episodes actively detected at 6-mo scheduled visit	19/210;	10/221;	OR: 2.099	(0.952–4.626)	0.476	
	Severe lower respiratory infections ACD at 6-mo scheduled visit	10/210;	2/221;	OR: 5.475*	(1.185–25.29)	0.183	
	Acute otitis media episodes passively detected at intercurrent clinic visits	41/231;	21/247;	OR: 2.322*	(1.326–4.066)	0.431	
	All admissions with evidence of malaria (spleen and/or slide positive)	58/231;	43/247;	OR: 1.591*	(1.021–2.352)	0.629	
	Admissions with clinical/symptomatic malaria	25/231;	17/247;	OR: 1.642	(0.862–3.127)	0.609	
	Admissions with severe lower respiratory infections (including TB)	67/231;	52/247;	OR: 1.532*	(1.009–2.326)	0.653	
	Admissions with acute otitis media	34/231;	19/247;	OR: 2.071*	(1.145–3.747)	0.483	
	Admissions with measles	25/231;	13/247;	OR: 2.184*	(1.089–4.381)	0.458	
	Days in hospital with severe LRTI/total infant days surveillance	629/66644;	402/71284	RR: 1.674*	—	0.597	
	Days in hospital with infectious disease/total infant days surveillance	997/66644;	623/71284	RR: 1.712*	—	0.584	
Menendez et al. (1997)	Clinical malaria episodes passively detected in main follow-up period	75/204;	81/207;	OR: 0.904	(0.607–1.347)	1.106	Odds ratio cannot be calculated from published data
	Any/none clinical malaria passively detected in post treatment follow-up	—	—	RR: 1.0	(0.7–1.3)	1.0	
	Admissions: main follow-up period: "rates per person-year at risk (number)"	0.75 (154);	0.98 (203);	RR: 0.94	(0.78–1.13)	1.064	
	Admissions in post treatment follow-up period: "rates"-same:	1.14 (84);	1.03 (78);	RR: 0.99	(0.78–1.25)	1.010	
	Outpatient visits (passive detection) in main follow-up period: "rates"-same:	6.67 (1360);	7.00 (1450);	RR: 0.99	(0.94–1.04)	1.010	Given "relative risk"
	Outpatient visits (passive detection) in 2nd follow-up period: "rate;"-same	5.86 (433);	5.28 (401);	RR: 1.10	(0.97–1.24)	0.909	Results used instead
Smith et al. (1989)	Active case detection: Fever with parasitaemia > 10/HPF	12/102;	2/99;	OR: 6.467*	(1.408–29.62)	0.155	Average denominators
Rice et al. (1998)[3]	Acute LRTI (cough + ≥1 day dyspnea + ≥1 day fever ACD)	62/307;	59/307;	OR: 1.064	(0.715–1.583)	0.940	
	Diarrhea (≥4 stools/d—active case detection)	152/307;	166/307;	OR: 0.833	(0.607–1.144)	1.201	
	Dysentery (diarrhea + ≥1 d of blood in stools—active case detection)	19/307;	25/307;	OR: 0.744	(0.401–1.382)	1.344	
Adam (1996)[3]	All illness-presumed infection (clinical assessment after trial-ACD)	232/366;	154/372;	OR: 2.451*	(1.822–3.296)	0.408	
	Clinical malaria (clinical assessment after trial—active case detection)	72/366;	49/372;	OR: 1.614*	(1.086–2.398)	0.620	
	Acute Respiratory infection (clinical assessment after trial-ACD)	47/366;	44/372;	OR: 1.098	(0.70–1.6)	0.911	
	Diarrhea (clinical assessment after trial—active case detection)	45/366;	50/372;	OR: 0.903	(0.6–1.3)	1.108	

TABLE 3 (*continued*)

Numerical tabulation of infectious morbidity outcomes for iron supplementation trials in malarial zones (where recorded)[1]

	Morbidity measure	Number #/Iron	Denom; Placebo	Odds ratio Fe:Plac	(95% confid intervals)	Inverse OR Plac:Fe	Comments
Gebreselassie (1996)	Clinical malaria (clinical assessment after trial—active case detection)	45/223;	31/222;	OR: 1.558	(0.944–2.570)	0.642	
Harvey et al. (1989)	Suspected clinical malaria from oral report (active case detection)	48/144;	52/144;	OR: 0.885	(0.544–1.437)	1.130	Oral reported morbidity
	Suspected gastro-enteritis from oral report (active case detection)	35/144;	27/144;	OR: 1.391	(0.790–2.450)	0.719	Oral reported morbidity
Murray et al. (1978)	Clinical malaria (clinical assessment end of supplementation—ACD)	13/71;	1/67;	OR: 14.79*	(1.877–116.57)	0.068	
Adam (1996)[2]	Clinical malaria (clinical assessment end of trial—active case detection)	88/363;	67/366;	OR: 1.428*	(1.00–2.042)	0.700	
	All illess—presumed infection (clinical assessment end of trial—ACD)	158/363;	124/366;	OR: 1.504*	(1.115–2.030)	0.665	
Hombergh (1996)	Extra attendance for clinical care (passive case detection)	14/50;	6/50;	RR: 2.33*	—	0.429	Odds ratio cannot be calculated from data multiple episodes per child
	All diagnoses (mixed active and passive case detection)	107/50;	65/50;	RR: 1.646*	—	0.608	
	Pneumonia (mixed active and passive case detection)	26/50;	5/50;	RR: 5.20*	—	0.192	
Berger et al. (2000)	Parasitized RBC $>$ 3000/mm^3; 0–3 mo of study (ACD/PCD) Rates/person · mo (n)	0.119 (84)	0.44 (79)	RR: 2.70 (NS)	—	0.370	Odds ratio cannot be calculated from data multiple episodes per child
	Parasitized RBC $>$ 3000/mm^3; 3–9 mo of study (ACD/PCD) Rates/person · mo (n)	0.036 (84)	0.00 (79)	RR: 3.6/0 (NS)	—	—	
	LRTI; 0–3 mo of study (ACD/PCD) Rates/person · mo (n)	0.101 (84)	0.123 (79)	RR: 0.821 (NS)	—	1.218	
	LRTI; 3–9 mo of study (ACD/PCD) Rates/person · mo (n)	0.051 (84)	0.076 (79)	RR: 0.671 (NS)	—	1.490	
	Diarrhea; 0–3 mo of study (ACD/PCD) Rates/person · mo (n)	0.138 (84)	0.096 (79)	RR: 1.438 (NS)	—	0.696	
	Diarrhea; 3–9 mo of study (ACD/PCD) Rates/person · mo (n)	0.096 (84)	0.049 (79)	RR:1.959 (NS)	—	0.510	

[1] OR/RR, odds ratio/relative risk; Fe/Plac, iron/placebo; #, where OR (95% int.) given, numerator refers to individuals with one or more morbid episodes; ACD/PCD, active/passive case detection; LRTI, lower respiratory tract infection. * Effect significant at 5% level or less.

Studies are ranked in order of design quality. Design criteria used: bias—adequacy of randomization, control, and blinding and follow-up retention; cohort definition and size; and methods of morbidity reporting.

[2] Unpublished studies.

tions in the control over the study group in a prospective trial of parenteral chelated iron medication administered to premature infants in Finland. No details were given in the letter.

In a controlled 2-y prospective study in the same population and same part of New Zealand as the study of Barry and Reeve (1977) (see above), Cantwell (1972) studied Polynesian neonates who had received 250 mg iron dextran at birth (in five daily doses) and apparently found an opposite effect (Table 1; Fig. 1), namely, 42 and 32% hospitalization rates for infections in control and iron dextran treatment groups, respectively. These effects are apparent in the recalculated OR, although they achieve significance only for the subset of respiratory infections (Table 1; Figs. 1–3). The obvious difference between these contrasting reports is in the time scale studied, i.e., the adverse effects reported in the neonates were immediate and, although serious, affected a relatively much smaller proportion of infants than Cantwell's finding of beneficial effects over a longer period. This contrast can be seen graphically in Figure 1.

Several more recent controlled studies have looked at the effect of iron-fortified milk on infectious morbidity. In one of these in Cape Town, Power and colleagues (1991) compared two levels of iron fortification of milk. The control was a standard formula (8.3 mg Fe/100 g), whereas the test milk powder had 40 mg Fe/100 g. The increased dose of iron resulted in better hematological outcome but the infectious morbidity outcomes were similar (Table 1).

In another study undertaken in Hungary by Hemminki and co-workers (1995), a birth cohort received iron-fortified milk (6.5 mg/L) and were followed for 1 y. Both passive and active follow-up by various levels of health care worker were combined. This intervention failed to find any differences in morbidity; however, the only morbidity recorded was upper respiratory and there were no hematological differences be-

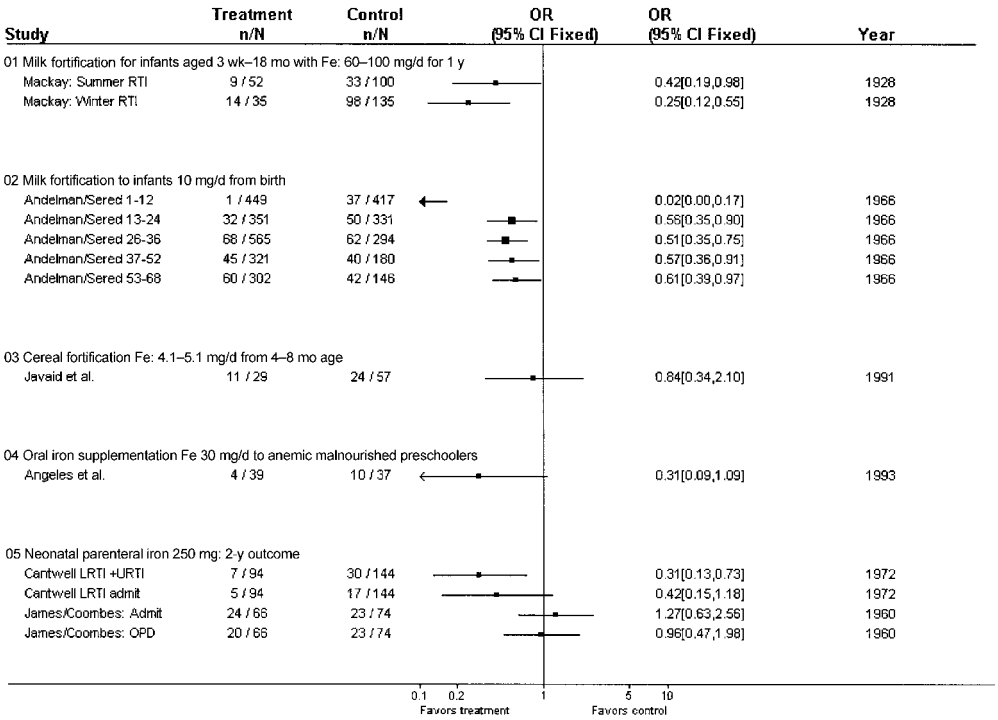

FIGURE 2 Iron trials in nonmalarious regions. Outcome: respiratory infections. Methods of administration: food fortification: infants (1–3: Andelman and Sered 1966, Javaid et al. 1991, MacKay 1928); oral supplementation: preschoolers (4: Angeles et al. 1993); parenteral: newborns (5: Cantwell 1972, James and Combes 1960). Methods of morbidity quantification: unblinded oral recall (1 and 2); field clinical assessment (3 and 4); prospective hospital based clinical assessment of serious infections (5); active case detection (1–4); prospective passive case detection (5), historical controls (1). LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection; OPD, outpatient detection.

tween intervention groups. For these reasons, this study is not included in tables.

Heresi and colleagues (1995) conducted a controlled study using iron fortification of full-fat powdered cow's milk (fortified with 15 mg Fe/100 g compared with unfortified milk) of infants in Santiago, Chile. Follow-up was from birth to 15 mo of age. By 9 mo of age, 15% of mothers had changed their children to breast milk alone. This latter group of children was

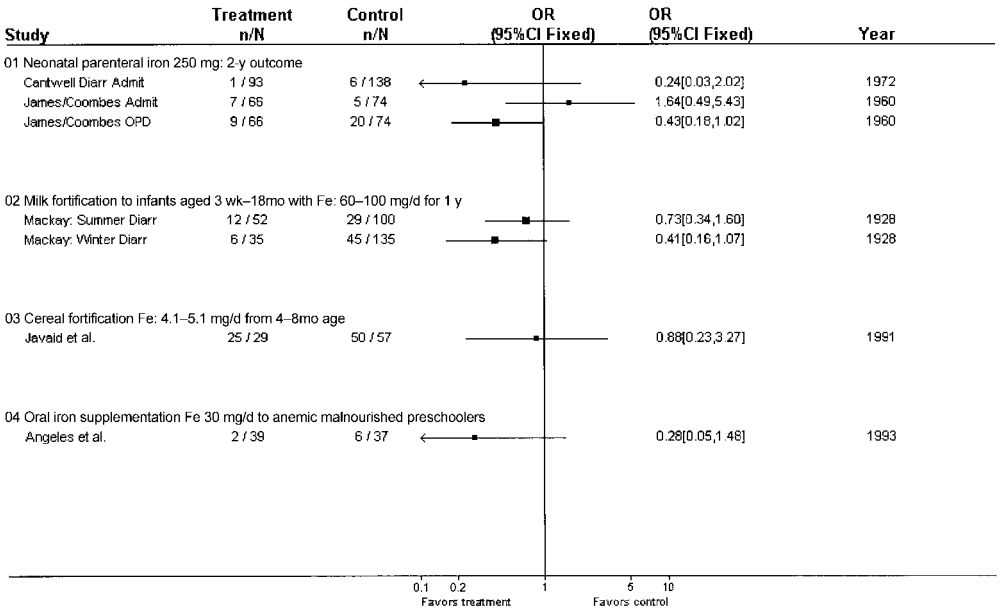

FIGURE 3 Iron trials in nonmalarious regions. Outcome: diarrheal infections (all types). method of administration: parenteral iron: infants (1: Cantwell 1972, James and Combes 1960); food fortification: infants (2: MacKay 1928 and 3: Javaid et al. 1991); oral supplementation: preschoolers (4: Angeles et al. 1993). Methods of morbidity quantification: hospital based clinical assessment of serious infections (1); unblinded oral recall with historical controls (2); field clinical assessment (3 and 4); prospective passive case detection (1); prospective active case detection (2–4). OPD, outpatient detection.

then observed as a statistically segregated group. Partial improvement of hematological status in the test group suggested that iron deficiency anemia in the control group was inadequately reversed by the level of supplementation. The authors interpreted the complex subdivided outcomes as showing a trend of lower infectious morbidity in the supplemented group and also in the noniron-deficient children from both groups. However, the former differences were not significant. The group that clearly did best with respect to lower infection rates was the group that had changed to breast milk alone; this group had significantly lower morbidity rates than did either the iron intervention or control group (Table 1).

Milk cereals with and without iron (mean daily intake 4.1–5.1 mg Fe) were given to groups of weaning infants (between 122 and 365 d of life) in a careful but complex 10-cell study conducted by Javaid and colleagues (1991) in Pakistan. There was a neighboring community control group with no nutritional supplementation. Although the iron was associated with a measurable effect on hematological values and infectious morbidity was reduced in all cereal-supplemented groups compared with the control group, there was no evidence of the iron intervention per se on such morbidity. It was concluded that the reduction in morbidity was a result of macronutrient supplementation (Table 1; Figs. 2, 3).

Three nonfood oral iron supplementation studies have given conflicting results in nonmalarious tropical regions. Chwang and colleagues (1988) gave oral ferrous sulfate [10 mg/(kg · d)] to Indonesian school children in a placebo-controlled, double-blind study for 12 wk. Infectious morbidity was scored on a composite scale. Children were assessed as anemic or nonanemic at the start of the study by hemoglobin and transferrin saturation, thus giving four cells. Those who were anemic were smaller and had a significantly higher morbidity score at the start. They were also the stratum that benefited from iron intervention in terms of significantly reduced infectious morbidity and improved growth and hematological status as assessed from the analysis of covariance. The presentation of their results does not allow calculation of OR; thus the study is not tabulated, but the ratio of morbidity scores by iron intervention in the anemic subgroup was an impressive 4.0. This is one of the few studies in the literature to show an effect of iron intervention on length velocity.

Another oral iron study (Fe 30 mg/d for 2 mo) in Indonesia was carried out with anemic malnourished preschoolers by Angeles and co-workers (1993). Reductions in rates of fever, respiratory infections and diarrhea were associated with iron therapy, although there were small cell numbers and these differences were not significant (Table 1; Figs. 2, 3). Conversely, Mitra and co-workers (1997) gave 125 mg of ferrous gluconate daily for 15 mo to half of a group of 349 Bangladeshi children aged 2–48 mo. No differences were noted in attack rates for diarrhea, dysentery or acute respiratory infections. The only exception to this was found on stratification of outcome by age. Children <1 y of age in the iron group had significantly more episodes of dysentery and more days of illness with this disease than their placebo counterparts. This last result could be important because it represents the only hint in the literature that oral iron may have any deleterious effects for infection at all in nonmalarious regions. Numbers of infants, however, were small (iron, $n = 34$; control, $n = 44$), and no overall effect was detected in the whole group (Table 1).

Overview of iron intervention studies in nonmalarious areas. In summary, iron intervention studies in nonmalarious regions can be divided into two types, i.e., parenteral and oral. Parenteral iron administration at birth carries significant risk of severe sepsis and meningitis (Barry and Reeve 1977, Farmer and Becroft 1976). Delay of this risky practice to the postneonatal period dramatically reduces such risks. Paradoxically, when parenterally dosed infants were followed long-term, subsequent morbidity due to respiratory, gastrointestinal and other infections was, on balance, reduced (Table 1; Fig. 1). This overall direction of benefit is shared with the oral supplementation studies (Figs. 1–3).

Oral iron supplementation was delivered by milk or cereal fortification in six of the studies reviewed. Two large studies carried out earlier in the past century both indicated that iron fortification carried an impressively lower risk of respiratory infections and a less clear reduction in diarrheal disease (Figs. 2, 3). This promise in these unreliable studies was not realized in four iron food-fortification studies performed in the 1990s that failed to show effects either way (Table 1). Perhaps the real message to be drawn from the latter studies was that breast milk is best. Although, in principle, more careful work is required in nonmalarious regions, it is unlikely in practice that much more will now be learned with fortification studies. There is a strong case for iron fortification of formula milk and no evidence at all that this fortification per se increases infectious morbidity.

If any area is understudied in nonmalarious regions, it is the effect of oral iron supplementation on infectious morbidity in breast-fed infants. Three oral iron therapy interventions to mainly older children gave conflicting results. Two interventions showed a reduction in infectious morbidity and a third did not detect any change except an increase in dysentery in infants.

The least that can be said of the evidence from iron supplementation studies in the nonmalarious areas in the 1990s is that there is little or no evidence of harm. The study of Chwang et al. 1988 was the only one to show clear evidence of benefit. From the public health point of view, arguments for oral iron supplementation in nonmalarious areas should be determined more by its other known benefits.

Long-term studies in malaria-endemic regions

Controlled studies of iron supplementation have been conducted in malarial countries since the late 1970s, with some comment about infectious outcome (Oppenheimer 1998). Many of these studies recorded important laboratory outcomes of the intervention, such as hemoglobin change and parasite prevalence. These surrogate outcomes have been dealt with elsewhere (Shankar et al. 2000) and are not discussed further here. Eleven studies had quantitative infectious morbidity outcome data in some form (Adam 1996, Berger et al. 2000, Gebreselassie 1996, Harvey et al. 1989, Menendez et al. 1997, Murray et al. 1978, Oppenheimer et al. 1986a and 1986b, Rice et al. unpublished data, 1998, Smith et al. 1989, van den Hombergh et al. 1996).

The earliest of the prospective studies, the report of Murray et al. (1978) of infectious recrudescence during iron therapy, has already been mentioned under immediate treatment effects (Tables 2 and 3; **Fig. 4**). This study followed up only for 30 d, the final observations coinciding with the end of supplementation.

Parenteral iron intervention. A large prospective, randomized, double-blind, placebo-controlled trial of parenteral iron supplementation in infancy was carried out in Papua New Guinea, in the early 1980s by Oppenheimer and colleagues (1984a, 1984b, 1986a and 1986b). It had been established that iron deficiency was prevalent among infants in the study population and that malarial transmission was intense. To

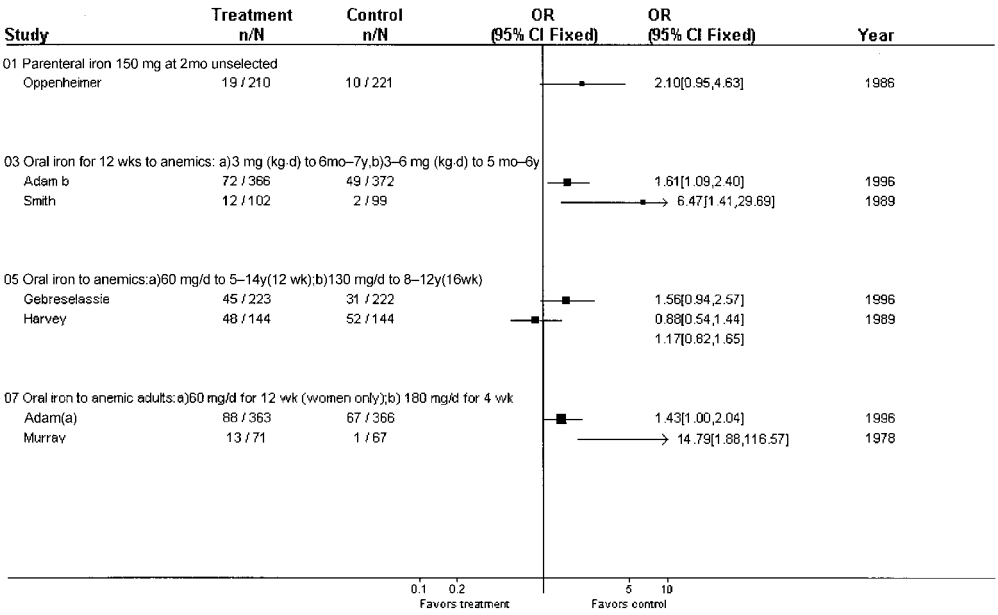

FIGURE 4 Iron trials in malarious regions. Outcome: clinical attacks of malaria. Method of administration: parenteral iron: infants (1: Oppenheimer et al. 1986a); Oral supplementation: anemic preschoolers (3: Adam 1996b, Smith et al. 1989); oral supplementation: anemic school children (5: Gebreselassie 1996, Harvey et al. 1989); oral supplementation: anemic adults (7: Adam 1996a, Murray et al. 1978). Method of morbidity quantification: prospective regular active case detection in field; field clinical + slide assessment (all).

avoid the known risks of iron therapy in the neonatal period (Barry and Reeve 1977), a single dose of iron dextran (150 mg elemental iron) was administered at 2 mo of age to the treatment group ($n = 236$); control infants ($n = 250$) received an injection of sterile pyrogen-free saline. Infants were reexamined and relevant blood samples were taken 1 wk after the injection and at 6 and 12 mo of age. All admissions to hospital were documented (Tables 2 and 3; Figs. 4–8).

Several results emerged. In contrast to the New Zealand studies of parenteral iron administration (Barry and Reeve 1977, Forman and Stiehm 1969), no significant differences in infectious morbidity rates were seen at the follow-up visit 1 wk after the injection of iron (data not shown). However, at 6 mo, clinical malaria (Fig. 4) and severe lower respiratory infections (**Fig. 5**) were more prevalent in the iron treatment group (Table 3). Acute otitis media was more frequent in self-presenting outpatient visits in the iron group; 25% of the iron treatment group had malaria-associated admissions to hospital in y 1 of life compared with 17% of the placebo group ($P < 0.05$) (Table 3; Fig. 5). Admissions with clinical symptomatic malaria, severe lower respiratory infections, measles and acute otitis media were all more frequent in the iron treatment group (Table 3; Fig. 5).

Increased malaria associated with increased pneumonia morbidity rates. Although increased malaria rates both in hospital admissions and in the field were the most clearly demonstrable morbid effect of iron supplementation found in this study, clinical attacks of malaria were a relatively less common primary reason for admission than acute lower respiratory infections (16 vs. 63%) (Table 3; **Fig. 6**). All 12 deaths in the study were due primarily to pneumonia (5 iron group, 7 placebo).

Rates of admission for pneumonia and time spent in hospital with pneumonia were higher in the iron dextran group

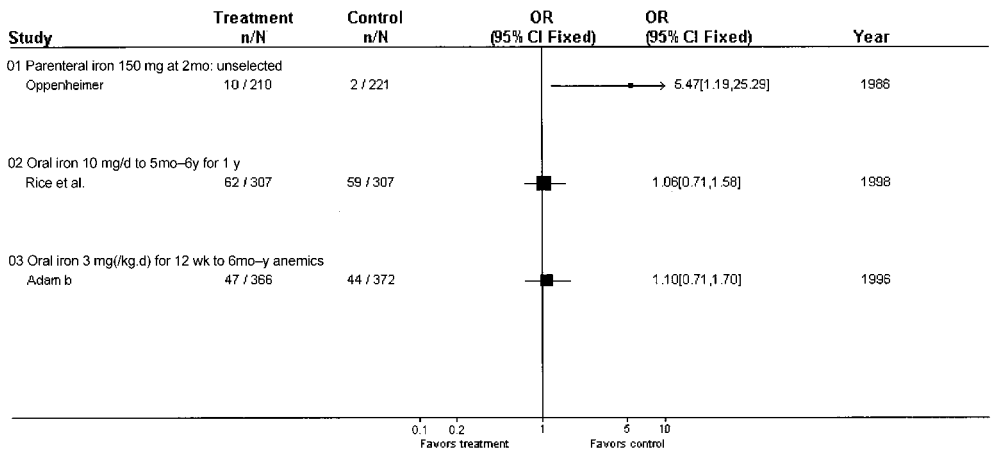

FIGURE 5 Iron trials in malarious regions. Outcome: respiratory infections. Method of administration: parenteral iron to infants (1: Oppenheimer et al. 1986a); oral supplementation anemic preschoolers (2: Rice et al. personal communication, and 3: Adam 1996). Method of morbidity quantification: prospective regular active case detection (all); full clinical assessment in field (1); oral recall (2 and 3).

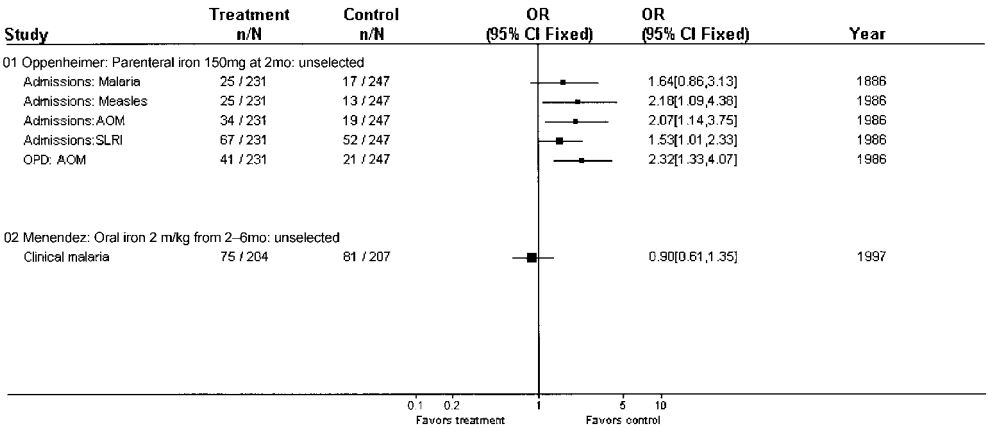

FIGURE 6 Iron trials in malarious regions. Outcome: passively detected infectious morbidity in age-defined cohorts of infants. Method of administration: parenteral iron (1: Oppenheimer et al. 1986a); oral supplementation (2: Menendez et al. 1997). Method of morbidity quantification: prospective passive case detection using clinic visits (OPD) and admissions for severe infection full clinical and laboratory assessment (1); oral recall (2). Abbreviations: AOM, acute otitis media; SLRI, severe lower respiratory infection; OPD, outpatient detection.

(Table 3; Fig. 6) (Oppenheimer et al. 1986b). Because this conflicts with the results of longitudinal studies reported previously in infants from nonmalarious areas, it is worth examining the possibility that malaria might have had an effect on susceptibility to pneumonia. Indirect evidence is available for this, i.e., 89% of pneumonia admissions had evidence of malaria (blood slide positive, significant splenomegaly or both), a much higher rate than that observed among the study children in the field. Support for the idea of a promoting effect of malaria on other infectious morbidity, particularly pneumonia, through a presumed influence on immune susceptibility comes from a recent study in the same community (Allen et al. 1997). Studies with the permethrin-impregnated bed net have also shown a dramatic reduction in nonmalarial as well as malarial infectious morbidity, again supporting the protean nature of malaria (Alonso et al. 1991). If such a close interaction between malaria and pneumonia is substantiated, it will go a long way to explain the opposite effects of iron supplementation on respiratory disease in temperate and tropical countries. It also underlines the importance of measuring all infectious morbidity, not just malaria.

Hyperferremic effects of parenteral iron are short-lived. It has been argued that any general interpretation of the results of the Oppenheimer study for iron intervention in malarious areas is limited because a parenteral iron preparation was used. This position may be overstated. At the current state of knowledge, the immediate hyperferraemic effects of parenteral iron do not last longer than several weeks (see above). Further, no significant morbidity difference was recorded at the 1-wk check after the injection, and clinically significant hyperferremia was not noted at the subsequent field follow-up visits up to 1 y of age. Differences in morbidity observed all relate to periods well after the intervention.

Oral iron intervention. *Effect of age and malarial immunity.* A more relevant issue is that the study group used by Oppenheimer was an age-defined cohort of infants aged 2 mo who may be regarded as less immune than other children in malaria-endemic areas. In contrast, in a report of a 16-wk study in the same area, Harvey et al. (1989) failed to show any adverse effects of oral iron supplementation to prepubescent schoolchildren, particularly in relation to malaria indices (Figs. 4 and **7**). Morbidity assessment, however, was based on mother's recall (Table 3). Harvey and colleagues speculated that acquired malarial immunity in their schoolchildren may have masked the potential interaction between iron and malaria. Harvey's report is now in a minority. Two subsequent intervention studies in schoolchildren that gave oral iron for anemia (Adam 1996, Smith et al. 1989) and a further two in adults (Adam 1996, Murray et al. 1978) have shown an increased risk of clinical malaria. One other showed a similar trend that did not achieve statistical significance (Table 3, Fig. 4) (Gebreselassie 1996).

The potential effect of age on immunity to malaria is actually a strong argument in favor of using age-defined cohorts in randomized controlled trials. The Tanzanian trial of Menendez et al. (1997) was the only other childhood trial in the literature to use an age cohort. All of the other studies reviewed used mixed age groups, spanning up to 5 or even up to 14 y, and generally did not stratify for age in analysis (Adam 1996, Berger et al. 2000, Gebreselassie 1996, Harvey et al. 1989, Rice et al. unpublished data, 1998, Smith et al. 1989). The Menendez et al. trial was also closest to the previous New Guinea study in that infants were started on daily oral iron at 8 wk of age and therapy was limited to 16 wk.

One further study of oral iron supplementation has just been published from work in Togo in West Africa (Berger et al. 2000). Oral iron [2 mg/(kg · d)] was administered for 3 mo to children aged 6–36 mo who were followed closely during supplementation and for 6 mo thereafter. The trial commenced from the beginning of the malaria transmission season and continued through to the next dry season. The authors concluded from lack of any significant morbidity differences between treatment groups that there was no risk. Relative risks of infectious morbidity associated with iron treatment estimated from data in the report varied, i.e., they were high for high density malarial parasitemia, raised for diarrheal disease and low (i.e., protective) for respiratory disease (Table 3). Numbers were too small ($n = 100$ iron and $n = 97$ placebo) and fell by 17.3% over the trial; it is therefore difficult to draw positive or negative conclusions with confidence from this study (Table 3) (Berger et al. 2000).

Selective anemia intervention or community-based supplementation? Of all reviewed trials with morbidity data, only the Oppenheimer, Menendez, Berger and Rice studies used unselected community-based cohorts. Also, the first two were the only studies to assess severe infectious morbidity requiring hospital admission. All of the other studies were effectively anemia treatment trials in that individuals with normal hemoglobin values were excluded. This exclusion could give an unrepresentative prediction of the outcome of an unselected

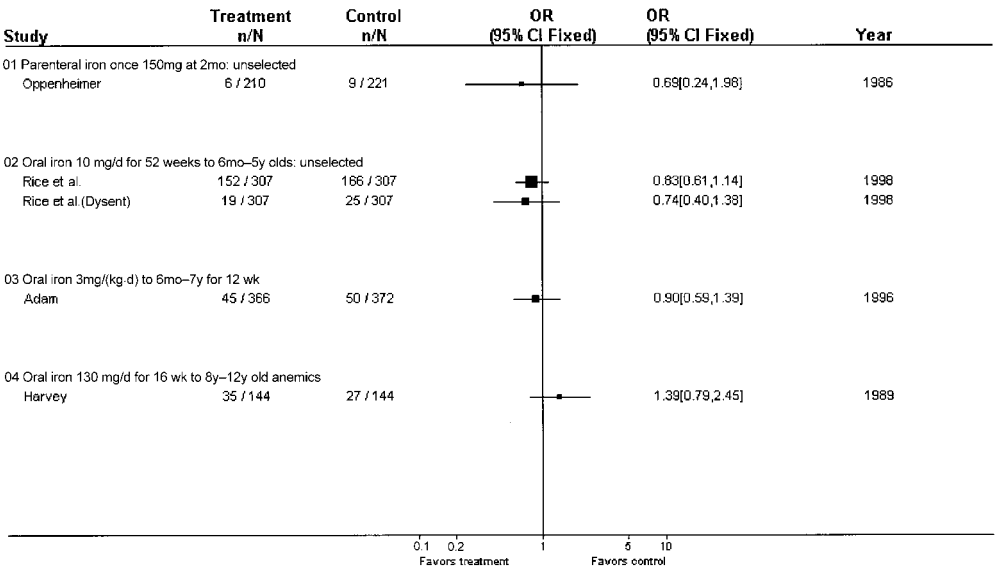

FIGURE 7 Iron trials in malarious regions. Outcome: diarrheal infections. Method of administration: parenteral iron to infants (1: Oppenheimer et al. 1986a); oral supplementation to anemic preschoolers (2: Rice et al. personal communication, and 3: Adam 1996); oral supplementation to anemic school children (4: Harvey et al. 1989). Method of morbidity quantification: prospective regular active case detection (all); full clinical assessment in field (1 and 3); oral recall (2 and 4)

community iron intervention. Furthermore, because the respective contribution of the common causes of anemia at the commencement of the trials such as malaria, iron deficiency and hemoglobinopathies (see below) were unknown, such studies are even more difficult to evaluate.

Effect of dose and timing. The timing and dose of oral iron may also be crucial, particularly in relation to risk of malarial infections at the time of administration. In the Menendez trial, a 2 mg/kg dose of iron was administered daily. The theoretical advantages to the infants of this scheme were as follows: *1*) iron was given as a limited dose and duration at a time when rapid hemoglobin synthesis ensured maximal use of the iron; and *2*) in these infants 16+ wk of age, any imbalance in body iron compartments resulting from supplementation would have been confined to the period of maternal immunological protection and would have settled before most infants had contracted their first malarial infection. There was no significant effect of the iron supplementation on subsequent malarial experience, but it raised hemoglobin levels. Respiratory disease rates were not specifically reported, but Menendez did not find any increase in morbidity in the iron group (Table 3; Fig. 6) (Menendez et al. 1997). In contrast, the study of Smith et al. (1989) was conducted in the Gambia and recruited children with anemia aged from 6 mo to 5 y. Causes of anemia varied and, although iron deficiency was prevalent, may also have included malaria. Half of these received therapeutic oral iron at 3–6 mg/kg for 12 wk during the period of maximal malaria transmission, whereas the others received placebo. Clinical malaria was more frequent in the iron group (Table 3).

Common hemoglobinopathies. Another factor that must be taken into account in such intervention studies is the interactions between the different globin chain disorders and the iron therapy. We have already seen above that these common inherited disorders may carry significant protection against clinical malaria and other infectious disease. Oppenheimer et al. (1987) noted that the deleterious effect of parenteral iron on susceptibility to malaria was largely masked in children with single-deletion α-thalassemia compared with normal children. Menendez and co-workers (1995), by contrast, found that in a placebo-controlled trial of oral iron in multigravid women, mothers with sickle trait (AS) genotype (and their babies) suffered deleterious effects whereas normal (AA) mothers benefited from iron. Because both these globin chain disorders themselves protect from malaria and reach very high polymorphic frequencies, possible interactions such as these must be taken into account in evaluation of intervention trials.

The Gambian study of Smith et al. (1989), for example, carried the highest risks of clinical malaria associated with iron therapy (Table 3; Fig. 4) Coincidentally the Gambia has, for Africa, an unusually low rate of deletional α-thalassemia [85% of the population have no deletions (Flint et al. 1993, Smith et al. 1989)]. In malaria-endemic parts of the continent, including East Africa (Oppenheimer, unpublished data), up to 50–70% of the population may carry or be homozygous for the deletion.

Malarious regions morbidity: overview of study design, confounding, and differing outcomes. A number of design differences and confounders may thus explain in part the conflicting morbidity results of the eight oral iron intervention trials involving infants and children in the tropics, both with and without malarial and iron-deficiency anemia, that measured clinical malarial morbidity. Of these, Adam's and Smith's studies, which were both conducted on preschool children during the malaria season and used 3–6 mg/(kg · d) iron, showed a significantly increased risk of clinical malaria. Two more studies showed a statistically nonsignificant increased risk. One of these (Berger et al. 2000) was carried out over a transmission season but had low numbers; the other (Gebreselassie 1996) had sufficient numbers with the lower 95% OR value at 0.94 but was carried out in older children and outside the transmission season. Of the two that failed to detect any difference, the study of Harvey et al. (1989) was conducted in older children with >90% α-thalassemia rates, was outside the transmission season, and used only mother's morbidity recall. The other study was that of Menendez (1997), which used low dose iron in very young infants (Table 3; Fig. 4).

Both oral supplementation studies in anemic adults that

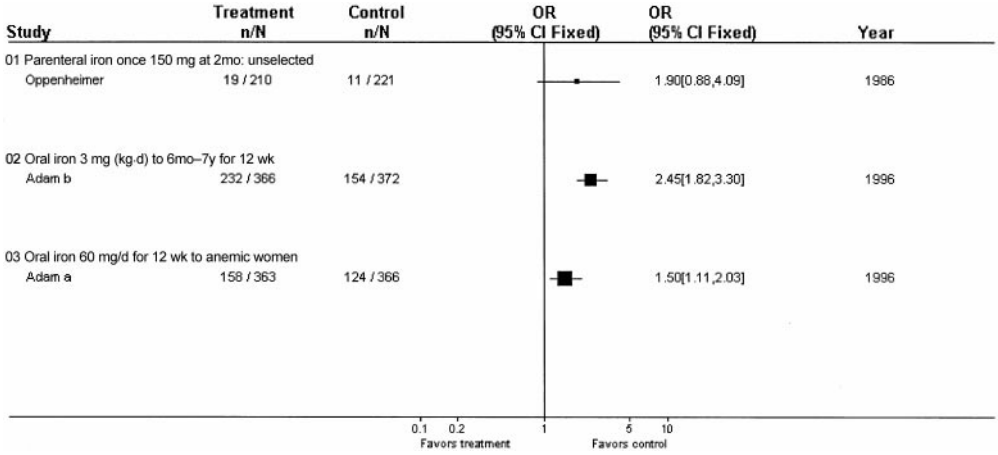

FIGURE 8 Iron trials in malarious regions. Outcome: other infectious disease. Method of administration: parenteral iron to infants (1: Oppenheimer et al. 1986a); oral supplementation to anemic preschoolers (2: Adam 1996b); oral supplementation to anemic women (3: Adam 1996a). Method of morbidity quantification: regular prospective active case detection with full clinical assessment in field (1–3)

measured clinical malaria showed significantly increased rates with iron. One of these (Murray et al. 1978), which showed recrudescence, has already been discussed. The other was carried out by Adam (1996) in Ethiopia.

Nonmalarial infectious morbidity. Seven oral iron anemia treatment trials (Adam 1996, Berger et al. 2000, Harvey et al. 1989, Menendez et al. 1997, Rice et al. unpublished data, 1998, van den Hombergh et al. 1996) measured nonmalarial infectious morbidity (A. L. Rice, personal communication). Three trials showed a significant iron-associated increase in risk of nonmalarial infectious morbidity (Table 3; **Fig. 8**) (Adam 1996, van den Hombergh et al. 1996). These were all studies that had shown an increase in malarial morbidity. van den Hombergh and colleagues (1996) showed a higher attendance for all diagnoses and for pneumonia specifically in children who had received iron (Table 3). Again, therapeutic doses of iron were used. Where measured, [4 oral studies (Adam 1996, Berger et al. 2000, Harvey et al. 1989, Rice et al. unpublished data, 1998)], there were no significant differences or trends for diarrheal disease (Fig. 7). None of the 10 oral trials showed benefits of oral iron supplementation on infectious morbidity. There were insufficient deaths in any trial to draw any conclusions relating to the intervention.

Summary of all results for controlled studies in malarious areas. An overview of the multiplicity of clinical outcomes in these 11 diverse controlled studies of iron intervention in malarious regions (Table 3) showed the following: a significant increase in clinical malaria attack rates in 5 of 9 studies and no rate reductions (Fig. 4); a significant increase in clinical pneumonia rates in 2 of 5 studies with no rate reductions; a significant increase in other nonmalarial infectious disease in 4 of 8 studies with no rate reductions (Fig. 8); no significant differences for diarrheal disease (Fig. 7); a suggestion that iron therapy may carry more risk in immunocompromised groups; and circumstantial evidence that adverse effects may be enhanced during the malaria transmission season.

Is pregnancy a special case? Oral iron is a standard supplement in pregnancy in many places, and in many parts of the tropics, parenteral iron is still sometimes administered for practical reasons as presumptive treatment of anemia during pregnancy. A group that appears to have peculiarly lowered immunity to malaria in endemic areas are women in their first pregnancies. The poorly controlled study of Byles and D'Sa (1970), suggesting that parenteral iron increases malaria in pregnant women, was referred to above.

Susceptibility is at its greatest in the first and second trimesters and crucially in primigravidae (Brabin 1983). In this context, it was noted in an observational comparison in Papua New Guinea that treatment of anemia with total-dose iron infusion during pregnancy was associated, in primigravidae, with a higher OR of maternal perinatal malaria; in contrast, this effect was not seen in multigravidae. After controlling for confounders and covariates, the parenteral iron was shown to have no net beneficial effect on hemoglobin of any group (Oppenheimer 1986c).

Fleming et al. (1986) reported an elevated nonsignificant risk of infection in an iron supplementation trial of Nigerian primigravidae. The results of the trial of Menendez and coworkers (1995) using oral iron for multigravid Gambian women was referred to above. Because anemia during pregnancy in the tropics is commonly due to malaria, treatment with iron could carry an unrecognized risk to primigravid women and AS genotypes. This highlights a recurring problem for populations in malaria-endemic areas. Those groups of individuals with a high risk of anemia secondary to malaria (infants, toddlers and mothers) are also selectively more likely to receive iron either as a supplement or as presumptive treatment for anemia.

Apart from these caveats, little other relevant morbidity information exists for iron, malaria and other infections in pregnancy—in the tropics or elsewhere. Kulier and colleagues (1998) conducted a formal review of worldwide nutritional interventions in pregnancy, adopting the Cochrane approach to analysis of controlled trials. Maternal infection was specifically looked for as an outcome in iron supplementation trials—without success.

Does iron withdrawal alter malaria severity? With the clinical and experimental evidence for interactions between iron and malaria, several clinical trials of iron chelation in malaria have been published. In one of these, 28 asymptomatic parasitemic volunteers had significantly enhanced parasite clearance with desferrioxamine (DFO) compared with randomized control subjects. Recrudescence was common (Gordeuk 1992b). In another study, recovery time from deep coma was significantly shortened (by half) by the addition of intravenous DFO to the standard Quinine/Fansidar treatment regime in a randomized, double-blind, placebo-controlled trial in Zambia (Gordeuk 1992a). In addition, the rate of parasite clearance was doubled in the DFO group. Although indicating the close

relationship between iron and malaria, such studies cannot help predict the outcome of iron supplementation trials.

Causal relationships: do they exist in malarious regions?

For those studies in which increased risk of infectious disease was noted in malarious areas, OR associated with iron supplementation ranged from 1.5 to 6.5 with most <2. Because these were controlled, randomized intervention trials, causality could be inferred for differences in outcome. It is clear that total infectious morbidity and mortality must be measured in future iron intervention studies. Because there were no consistent means of comparing the iron status of the participants in the different trials, no comment can be made on whether the severity of iron deficiency is an effect modifier. On the other hand, there was weak circumstantial evidence that there may be a dose-related risk of oral iron in these studies. In Oppenheimer's study, community-based hematological values (excepting birth hemoglobin) had no useful predictive value for subsequent infectious morbidity in the placebo group.

Because no useful effect of iron supplementation on infectious morbidity could be shown and negative effects were shown, these have to be balanced in a risk-benefit analysis against any known benefits of iron supplementation in these populations.

Is there a connection between human immunodeficiency virus and iron?

Malaria is not the only prevalent tropical infection to interact deleteriously with iron. Although knowledge is at an early stage, there are several indications that the effect of mass iron supplementation on the natural history of human immunodeficiency virus (HIV) infections must be investigated urgently, particularly in some parts of Africa where subsets of the population have potentially toxic iron overload. Iron chelation with DFO in vitro inhibits HIV-1 replication and reduces the rate of spontaneous apoptosis of CD_4+ lymphocytes. The dose and efficacy of DFO in chelation therapy has been shown to affect the rate of HIV progression in people with thalassemia. In studies of the prophylaxis of *Pneumocystis carinii* in patients with HIV disease, 30 mg of elemental iron daily for 6 mo was shown to be associated with excess mortality (Boelart et al. 1997).

SUMMARY

Is there evidence of a relationship between iron deficiency and susceptibility to infection?

Despite proven reversible functional immunological defects, a clinically important relationship between states of iron deficiency and susceptibility to infections remains controversial, difficult to prove and may depend on other immune factors in the community. Experimental and in vitro animal studies suggest that organisms that spend part of their life cycle intracellularly, such as plasmodia, mycobacteria and invasive salmonellae, may be enhanced by iron therapy. Evidence is scanty, indirect and inconclusive that iron deficiency may protect from infection in certain malaria-endemic situations or that it may enhance acute and chronic infections in nonmalarious countries. With the possible exception of decreased susceptibility to malaria-related disease, HIV and tuberculosis, the relevant immunological effects of iron deficiency itself appear to be mild compared with the clinical immunodeficiency syndromes. This should be borne in mind when assessing the effects of any exogenous iron administration because the net effects of the intervention per se may be deleterious and dose related.

What is the effect of iron administration?

Parenteral iron treatment is associated with life-threatening sepsis when given in the early neonatal period. There is no systematic evidence for this effect later in childhood or adult life.

Iron fortification of milk in nonmalarious regions was, in older and poorly controlled studies, associated with fewer respiratory infections in disadvantaged populations of nonmalaria-endemic regions. However, in more recent studies in these situations, it appears that breast milk confers greater advantages than powdered milk, iron fortified or otherwise.

Oral iron given as a supplement without food in nonmalarious areas may reduce infectious morbidity in disadvantaged populations. The effects of oral iron supplementation on infection in breast-fed infants have not been studied systematically in nonmalarious regions.

Oral iron supplementation in the tropics in children of all ages in doses >2 mg/(kg · d) has been associated with increased risk of clinical malaria and other infections including pneumonia. In several studies that did not show this effect, factors such as lower dose iron, immunity and the presence of hemoglobinopathy were regarded as protective. This suggests a dose-related, immunity-modified effect. In the treatment of severe anemia, when malaria is or may be a cause, low efficacy of the concurrent malaria treatment may be insufficient to prevent malarial interactions with therapeutic doses of iron. Although a number of studies indicate an increased risk of infection associated with oral iron in the tropics, there are no such studies showing a reduction in infections.

Recommendations

Given the present incomplete knowledge of the interactions of iron and infection, what recommendations can be given to health planners and pediatricians?

- Iron dextran prophylaxis to newborn infants (previously a common practice in both malarious and nonmalarious areas) is contraindicated.
- Presumptive treatment of anemia in malarious areas with parenteral iron is contraindicated.
- Oral iron supplementation has not been shown to cause an increased risk of infection in any age group in nonmalarious countries. Older reports suggest that infectious morbidity could be halved, although few later studies have confirmed this. The case for such intervention would therefore have to be made by other beneficial outcomes. Although breast milk is preferable to fortified powdered milk, further studies would be needed to assess the benefit in terms of infectious disease, if any, of oral iron supplementation to breast-fed infants.
- Oral iron supplementation in malarious regions may carry up to a 50% increased risk of clinical malaria if given in therapeutic doses at times of malaria transmission. If there are any general principles that may be inferred for health planners wishing to conduct iron interventions in malaria-endemic areas, they are the following: *1*) beware populations with potentially compromised immunity (especially to malaria), for example, HIV carriers, primigravidae and young infants; *2*) beware high dose supplementation; *3*) beware supplementation during the peak malaria transmission season; *4*) beware known AS and

SS genotypes; *4*) beware interpreting low population mean hemoglobin values as resulting solely from iron deficiency. Clearly, it may not be appropriate to withhold supplementation to some of the above risk groups. In these cases, proven strategies may be applied. For example, iron treatment for anemia in a malarious area should be covered or preceded by effective antimalarial therapy. Iron therapy should be oral and, where possible, the decision to use iron should be based on laboratory evaluation of the cause of anemia—if not in the individual then at least in the community. Lower dosage should be used where there are risk factors. More carefully conducted prospective studies in populations with iron deficiency as the known dominant etiologic factor (and assessing all morbidity) are required to assess the risks in these groups.

- An evaluation of the effect of iron fortification in which the daily iron doses would be much smaller and the concurrent administration of zinc are two avenues worth pursuing. Also important will be evaluating the effect of intermittent iron administration because this method of intervention is being advocated in certain settings (Black 1998).
- Oral iron supplementation in therapeutic doses to older immune children and adults in malarious regions may also carry up to a 50% increased risk of other infectious disease. Additional controlled clinical studies are clearly warranted before definite recommendations are made.
- Studies are urgently needed in both malarious and nonmalarious regions to assess the effect of iron deficiency and iron supplementation on morbidity and mortality due to HIV, tuberculosis and typhoid.

Policies for standard presumptive treatment for anemia at the primary health care level in developing countries must be reviewed with particular reference to age group, malarial endemicity, prevalence of globin chain disorders and identifiable causes, preferably with the aid of results from systematic reviews of randomized controlled studies.

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DISCUSSION

Participants: Lynch, Sazawal, Schultink, Oppenheimer, Habicht, Allen, De Benoist, Brabin, Stoltzfus

Dr. Lynch: So, this is the first time we are asking ourselves, is it an advantage to have a disorder that we all think for other reasons is a significant disadvantage. I would like to highlight two issues. First is the issue of whether there is an effect of iron deficiency on immunity and the virulence of pathogens. The second issue is the effect of iron supplementation on the prevalence and clinical course of infectious disorders.

These are not necessarily the same issue—they may well be different issues—and the opportunities that we have for changing the course of iron deficiency are different at different times. If you are presented with someone with severe iron deficiency, you are stuck with high doses. High doses may be very bad. If you can get yourself into a situation where that does not happen, you may be able to avoid the pathology that you are inducing by the way in which you have to try to correct the abnormality.

There is a new area here that is important and unstudied, and this is this labile intracellular pool. There is much more reason now to think that that is an important issue. Certainly for malaria—it seems to be the pool from which malaria gets its iron—and probably for tuberculosis and possibly for human immunodeficiency virus (HIV). There is another pool that is not often talked about by us but often is by the iron overload people, and that is the nontransferrin-bound iron pool. These are the pools that individuals are manipulating in trying to treat malaria and infections. This is the pool that desferrioxamine gets into. This is also the pool that potentially—say this

partly provocatively—you may be able to alter dramatically by giving big doses of iron. If you give iron to an iron-deficient person, there is a marked rise in the serum iron level and transferrin saturation. There may be a transitory but big change in this iron pool. So, that is one area that may merit more attention from the experimentalists.

There certainly are some articles appearing now suggesting that iron deficiency could theoretically have a protective effect in malaria, HIV disease and tuberculosis. The reason that I bring it up is just to make sure that everyone here is aware of this other lobby for removing iron from individuals to protect them against infection. Now, having said that, I think that the major analysis that Dr. Oppenheimer was able to do—and this is clearly because of the available data—was really not so much on the effect of iron status on infection, but more the effect of iron supplementation on infection.

There really is not any substantive evidence to suggest that there is truly an effect of nutritional immunity—that iron deficiency is indeed protective. I would think that that applies to the HIV and tuberculosis issue, and also to the malaria. The malaria issue is related to anemia, which is probably a poor surrogate for iron deficiency.

In terms of iron supplementation, the question is whether we need to do it and, if we do need to do it, perhaps what we really should be focusing on more is the method of correcting iron deficiency—in other words, the method of supplementation. There are important issues here. Doses in the past probably have been much too big. There is real reason to suspect, although it has not been proven, that the dose is an important issue in terms of malaria recrudescence and so on. There is also the important issue of whether these large doses have important effects on other nutrients. The one, speculatively, that is very attractive is zinc. Zinc shares these pathways intracellularly. Possibly it is an effect on zinc that is making malaria more prevalent.

I wanted to put in a plug for iron fortification, because iron supplementation might not be necessary. You might not have to give these big doses if you could put in smaller doses earlier or over a longer period. One point that I have forgotten to mention in terms of administration is the other big issue in this area—intermittent administration, where large doses are given every week. It will be important to look at that as well, in terms of effects on malaria.

Then, we are back to the question of treating iron deficiency and not only anemia. So, we are back to the question of who gets looked at in terms of iron supplementation and the importance of specific indicators, not for anemia but for iron deficiency.

Dr. Sazawal: You do not have any data from developing countries in nonmalarious areas, and the only study that you have shows an increased risk. It seems there are no data from south Asia and other developing countries evaluating increased morbidity in children with iron supplementation, apart from malaria. That is an area that needs to be looked at.

I agree that evidence is clear that iron supplementation does not cause a reduction in malaria, diarrhea, pneumonia, or other morbidity, and that is clearly evidenced. However, the evidence is not clear-cut about a possible increase. If there is, we need to figure out what it is. If there is an increased risk, we need to be sure what that increased risk is and quantify that increased risk to the extent possible.

There is also an issue of separating severe morbidity from nonsevere morbidity. I come from the zinc research area. One of the recent studies that we did was a randomized, double blind, well-controlled zinc trial in low-birth-weight infants. The morbidity—if you looked at diarrhea or pneumonia—remained the same or increased. Cough increased significantly, but zinc reduced mortality by 45%. You could have a scenario where the overall morbidity may increase or be the same, and you could still have an effect on severe morbidity as well as mortality—and those need to be differentiated.

Dr. Schultink: I would like to question you about the recommendations. A number of countries in West Africa were considering doing some iron supplementation program in preschool children. If you look at your recommendations, you have four bewares—beware compromised immunity, beware the risk of high dose without defining what you consider high dose, beware supplementation during malaria—and Africa is loaded with malaria—and beware of hemoglobin AS genotypes. According to you, should we not support these programs?

Dr. Oppenheimer: I am not saying these are contraindications. I am saying that if you are planning an intervention, you should take those risk factors into account.

Dr. Schultink: In practice, what would you do in those cases? I want to push you a little bit.

Dr. Habicht: A low dose is one answer. It seems that if preventive supplementation is at a reasonably low dose, there is no contraindication anywhere.

Dr. Oppenheimer: I think one should put it all together, if you are planning an intervention in a particular country or a particular region of that country. Because not all countries have the same amount of malaria and because some have mountains and some have lowlands, you should know the endemicity of malaria in the population that you are supplementing. You should know the frequency of the genetic disorders. You should know the degree of iron deficiency in that population. In order to know the degree of iron deficiency, regional surveys should be conducted to assess the real contribution of iron deficiency. So, when I say beware, it is that you should know a lot more about the population if you are planning to do an intervention. I do not mean not to do intervention.

Dr. Schultink: Of course, you will not jump into this just like that. There is apparently iron deficiency. We do not know about the genotyping, I have to admit.

The main issue here seems to be the increased risk of malaria. What I understand is that if you give a low dose—and the dose we are recommending at the moment is about something like 10–12 mg/d, which is even lower than 2 mg/(kg · d)—I understand that the risks of increasing malaria risk and severity are relatively low. Is that correct?

Dr. Oppenheimer: That could be implied from these results. I am not going to definitely say it as that.

Dr. Allen: We did a study in Mexico in which we gave 20 mg/d to preschoolers. We had an increase in respiratory infections.

Dr. Habicht: That is a real problem. Upper-respiratory infection always increases with improved nutrition. We have seen that now with zinc. That is uniform, and it is a real trap to say that is an increase in morbidity. That is an increase in symptomatology. It is simply a reflection of a better immune response to the disease.

Dr. Allen: It still should be included, with that comment made.

Dr. De Benoist: A more general question about the treatment of anemia. It could be a misdirection of iron supplements. What is the rationale for giving iron supplements to malaria patients, especially if iron is not always safe? Is the malaria treatment itself not enough? Is this really iron deficiency in the very young?

Dr. Oppenheimer: Ideally, you should be in a position to

determine the cause of anemia before you give the treatment. In the real situation, you cannot. In a field hospital in Africa, you are not in that position. I do not agree that one should routinely give iron with the antimalarials as a presumptive treatment for malaria if you have reason to suspect that the individual is suffering from malaria rather than iron deficiency. You should treat presumptively on what you think the cause of the anemia is and on the basis of what evidence you have. That evidence would include blood slide, enlarged spleen and also the age group of the child. The cause of anemia under in children under age 1 y in an endemic area is predominantly malaria. You would be interfering to give iron presumptively before you treated for malaria.

Dr. Brabin: Malaria in endemic situations is the main component in young children, but iron deficiency, and perhaps severe iron deficiency, is very likely to be very substantial in that group. Our cohort study in Malawi showed that there was a highly significant association between postneonatal infant mortality and iron deficiency. So, we have to be aware that it may be more substantial.

My clinical question relates to when you are faced with a baby who has hemoglobin of 60 g/L and about 9 mo of age and you try to make the diagnosis of the basis for the anemia when there are no parasites in the blood. I am putting that question to you because it is not uncommon. They may have just taken an antimalarial the week before, but we do not know for certain. Supplementation might be safe, but is it safe to give therapeutic doses of iron to these children? The therapeutic dose of iron, which I would not call high dose, can be in the range of 5–6 mg/(kg · d).

Dr. Stoltzfus: The current recommendations are, if you have a severe anemia, which we define as a hemoglobin <70 g/L, and you are in a malaria-endemic area, you give both at the same time. We did not specify the antimalarial. We said to give what is considered the standard of care in your situation. You are going to do the best you can. Even if you are in a chloroquin-resistant area and chloroquin is all you have, then you are going to use chloroquin. The idea is, while you have the child there and you are seeing a child with a hemoglobin of, say 50 g/L, you do everything that you can. That is going to include an antimalarial and a therapeutic iron dose, which by the current guidelines from the World Health Organization, International Nutritional Anemia Consultative Group, and United Nations Children's Fund is ~20 mg/d, I think. If hookworm is endemic and the child is older than 2 y, you give mebendazole or albendazole at the same time.

Dr. Sazawal: What is the evidence against giving a lower dose of iron if malaria is endemic?

Dr. Stoltzfus: Those therapeutic recommendations were the judgment of a group of people. To have them empirically evaluated would be a tremendous service—to look at the cure rates—and something that some of us have wanted to do for a long time. It has not been done.

Dr. Lynch: Remember that when you are taking an anemic child with a hemoglobin of 50 g/L, curing the malaria to cure the anemia, you do need iron to rebuild the normal hemoglobin. Unless that child has a very high iron store, almost by definition, the child will be iron deficient once you have taken away the cause for the low hemoglobin. I think it would be wrong to say all of those children are not iron deficient. I think it is very likely most of them, indeed, will be very obviously iron deficient once they try to rebuild the hemoglobin.