Summary

Some researchers have hypothesized that iron status may be an important determinant of infection risk, and particularly that low iron status may protect against malaria and other infectious diseases. Conversely, they hypothesize that iron supplementation and fortification may increase the risk of malaria and other infectious diseases.[1] To evaluate this hypothesis, we considered four types of evidence:

- Basic science research that evaluates the biological plausibility of the hypothesis.
- Observational studies that evaluate the relationship between iron status and risk of malaria infection.
- Randomized controlled trials (RCTs) that evaluate the impact of iron supplementation and fortification on the risk of malaria and all-cause mortality.
- RCTs that evaluate the impact of iron supplementation and fortification on the risk of non-malaria infections, focusing particularly on diarrhea and respiratory tract infections.[2]

This evidence leads us to the following conclusions:

- It is biologically plausible that iron status impacts infectious disease risk, although it is not obvious *a priori* whether iron supplementation in those who are deficient should increase or decrease infection risk, and this may depend on contextual factors such as the dose of supplement and the specific disease in question.
- Observational studies often suggest that people with low iron status are at a lower risk of malaria, and this relationship is difficult to explain by confounding.
- RCTs suggest that iron supplementation probably does not increase malaria risk, although it may do so in areas without prevention and treatment services. We are more uncertain about the latter conclusion than the former.
- RCTs do not suggest that iron supplementation increases all-cause mortality, although the evidence underlying this conclusion is limited.
- RCTs do not suggest that iron fortification increases malaria risk, although limitations of this evidence make our conclusion uncertain.
- RCTs suggest that iron supplementation increases the risk of gastrointestinal illness including diarrhea, but has little or no effect on the overall rate of non-malaria illness or on other prevalent categories of non-malaria illness including respiratory tract infections.
- RCTs on iron fortification report mixed results, but we do not believe they provide compelling evidence that fortification increases the risk of non-malaria illness.

---

[1] "To minimize the risk of infection, the physiology of these children has adapted to actively exclude iron much of the time, which is validated by the fact that rare genetic variants in the hepcidin-ferroportin pathway lead to iron overload even in people on low-iron diets. Second, because so much evolutionary experience has been distilled into extensive genomic investment in mechanisms mediating the host-pathogen competition for iron, it may be hazardous to intentionally override such processes by administration of excess iron… If iron deficiency is protective, reversing such deficiency would be expected to enhance malaria susceptibility as previously demonstrated." Prentice et al. 2013.

[2] Since they are the leading non-malaria causes of infectious disease mortality in low-income settings.

Overall, there appears to be little compelling evidence that iron supplementation or fortification increase the risk of malaria or non-malaria infections, with the exception of 1) diarrhea, and 2) possibly malaria in areas without prevention and treatment services.

However, two observations continue to give us pause. First, the inverse association between iron status and malaria infection risk in many observational studies. Second, the findings of Sazawal et al. 2006,[3] a large RCT suggesting that iron plus folic acid supplementation leads to excess hospitalization or mortality risk in a malaria-endemic region with malaria treatment services.[4] It remains possible that iron plus folic acid supplementation has larger adverse effects on malaria risk than either alone.

Background and biological plausibility

Iron is an essential mineral not only for humans, but also for our pathogens.[5] This includes the malaria parasite, which requires iron to grow and reproduce; the two cell types it inhabits-- red blood cells and liver cells-- are rich in this mineral.[6] In addition, free iron is a powerful catalyst for damaging free radical reactions. Presumably for these reasons, iron in the body is tightly sequestered by several types of proteins.[7]

The body reacts to infection by reducing iron levels in extracellular fluids, in red blood cell hemoglobin, and in liver cells, restricting its availability to many pathogens.[8] This process is coordinated by the secretion of the hormone hepcidin, predominantly by liver cells, in response

---

[3] Sazawal et al. 2006.

[4] Commonly used antimalarial drugs interfere with folate metabolism of the malaria parasite, so it is possible that folic acid supplementation undermines their effectiveness. However, a subgroup analysis of Sazawal et al. 2006, Sazawal et al. 2014, did not identify an association between folic acid supplementation, iron supplementation, and antimalarial treatment outcome in this context. This RCT used a relatively low dose of folic acid.

[5] "Almost all microorganisms are dependent on iron to a greater or lesser extent. This appears to be true for most human pathogens, and, in competition with the host's evolution of iron-withholding strategies, they have evolved an array of mechanisms for scavenging iron." Drakesmith and Prentice 2012, Pg. 768.

[6] "Plasmodium proliferation requires iron, both during the clinically silent liver stage of growth and in the disease-associated phase of erythrocyte infection." Spottiswoode and Drakesmith 2014, abstract.

[7] "Unbound iron or heme (released during constitutive or infectious hemolytic conditions), as well as providing the most critical growth-limiting nutrient to potential pathogens, can generate toxic free radicals that would cause host tissue damage if not contained. Systems have therefore evolved to ensure that iron and heme are tightly chaperoned. In humans, the dominant chaperone proteins are transferrin, lactoferrin, and ferritin for iron; haptoglobin for hemoglobin; and hemopexin for heme. These are regulated according to need and participate in receptor-mediated uptake by target cells." Drakesmith and Prentice 2012, Pg. 768.

[8] "Hepcidin's mode of action is to bind ferroportin and induce its degradation, thus inhibiting cellular iron efflux (10). Hepcidin exerts control over systemic iron trafficking by regulating the transfer of dietary, recycled, and stored iron from intracellular compartments to extracellular fluid" Drakesmith and Prentice 2012, Pg. 769. Also see figure 3.

to inflammatory signals.[9] The human body reacts to malaria infection by secreting hepcidin.[10,11] Since the body appears to treat iron as a liability in the context of infection, it seems likely that it is a determinant of infection risk.

The following observations further support this hypothesis:

- People with hereditary hemochromatosis, a genetic disorder that causes excess iron accumulation, have an increased risk of certain infections. Since several mechanisms may be involved, it is not clear that higher iron availability to pathogens is the primary cause of this increased risk.[12]
- Experiments suggest that malaria parasites infect red blood cells from people with iron deficiency less efficiently than those from people who are iron replete.[13]
- Taking a high-dose iron supplement (2 mg/kg body weight; 130 mg total iron as ferrous sulfate) causes "markedly elevated" growth of pathogenic bacteria in *ex vivo* human blood plasma[14]. This is the same dose of iron that is most often used in iron supplementation studies in low-income settings.[15] It is worthwhile to note that large doses of highly bioavailable iron may overload the ability of iron-binding proteins to

---

[9] "Although many molecular pathways are involved, the current thinking is that the circulating peptide hormone hepcidin, produced predominantly by hepatocytes, is hierarchically the master regulator [of iron metabolism]... Hepcidin expression is upregulated during inflammation." Drakesmith and Prentice 2012, Pg. 769.

[10] "Key to understanding the pathophysiology of iron metabolism in malaria is the activity of the iron regulatory hormone hepcidin. Hepcidin is upregulated during blood-stage parasitemia and likely mediates much of the iron redistribution that accompanies disease." Spottiswoode and Drakesmith 2014, abstract.

[11] Drakesmith and Prentice 2012, figure 3.

[12] "Jones suggested a possible link between infection and shock in hemochromatosis as one patient was found to have E. coli bacteremia. Since that time there have been numerous reports of patients with hemochromatosis having increased susceptibility to infections.Various infections caused by organisms including Vibriovulnificus, non-01 Vibrio cholerae, E. coli, Yersinia enterocolitica and pseudotuberculosis, L. monocytogenes, P. shigelloides, G. haemolysans, cytomegalovirus, hepatitis B, C, and G virus, and HIV have been reported in association with hemochromatosis. Fungi including A. fumigatus and Rhizopus species have also been described (Table 2). There is an article in German that describes parvovirus in association with hemochromatosis. A multitude of problems likely contribute to the increased susceptibility to infection in these patients. The very high transferrin saturations attained in patients with iron overload states compromise bacteriostatic properties. In the presence of excessive iron, pathogens can much more readily procure iron from molecules of transferrin. In such cases, even microbial strains that are not ordinarily virulent can cause illness. In addition, iron overload compromises the ability of phagocytic cells." Khan et al. 2007, Pg. 484.

[13] "Here, using an in vitro parasite culture system with erythrocytes from iron-deficient and replete human donors, we demonstrate that Plasmodium falciparum infects iron-deficient erythrocytes less efficiently." Clark et al. 2014, abstract.

[14] "We here investigated the ex vivo growth characteristics of exemplar sentinel bacteria in adult sera collected before and 4 h after oral supplementation with 2 mg/kg iron as ferrous sulfate. Escherichia coli, Yersinia enterocolitica and Salmonella enterica serovar Typhimurium (all gram-negative bacteria) and Staphylococcus epidermidis (gram-positive) showed markedly elevated growth in serum collected after iron supplementation." Cross et al. 2015, abstract.

[15] "The mean iron supplementation dose was 2 mg/kd/day and the mean duration of treatment was 4.5 months (1.5 to 12 months)." Okebe et al. 2011, Pg. 12.

effectively sequester iron, making this finding more applicable to supplementation than naturally iron-containing foods or fortification.[16] This concern may also apply to iron injections.[17]

On the other hand, iron is important for normal immune function. Iron deficiency impairs certain aspects of immunity, and supplementation restores them[18,19] It is therefore not obvious *a priori* whether iron supplementation should improve or impair overall infection risk, and it may depend on contextual factors such as baseline iron status, the dose of iron, how rapidly the iron is absorbed, and the specific infectious disease(s) of concern. However, it is biologically plausible that iron status might impact the risk of infection by malaria parasites and other disease organisms.

Impact of iron supplementation and fortification on malaria risk

Note: Parts of this section are drawn from my previous work on iron.

Observational studies

We performed a quick literature search focusing on review papers. Our understanding is that observational studies often report that people with lower iron status are less likely to be infected

---

[16] "Oral iron supplementation provides a nonphysiological bolus dose of highly absorbable iron that can temporarily overwhelm the regulatory and chaperone mechanisms that normally mediate the safe passage of iron from enterocytes to the target tissues." Drakesmith and Prentice 2012, Pg. 768.

[17] "During a five-year period the incidence of neonatal sepsis was 20 times higher in Polynesian newborns compared with European newborns (11 per 1,000 vs. 0.6 per 1,000 total births). This high incidence in Polynesians was confined to a period when the infants were being given intramuscular iron dextran. When the iron administration was stopped the incidence of disease in Polynesians decreased from 17 per 1,000 to 2.7 per 1,000 total births. An analysis of the Polynesian iron-treated and non-iron-treated groups showed a statistically significant difference in the incidence of sepsis, the type of causative organism, and mortality." Barry and Reeve 1997, abstract.

[18] "Of greatest relevance to infectious disease stress, iron deficiency can increase susceptibility to infection by compromising immune function. Although antibody-mediated immunity is largely unaffected by iron status, cell-mediated immunity (CMI) is impaired by iron deficiency (Chandra and Newberne, 1977; Field et al., 2002; Joynson et al., 1972). The extent of deficiency necessary to impact CMI is unclear: some argue that even mild and moderate levels of iron deficiency cause some CMI deficit (Joynson et al., 1972; Thibault et al., 1993), while others question the existence and importance of such an effect short of anemia (Field et al., 2002; Oppenheimer, 2001)." Wander et al. 2009, Pg. 2.

[19] "Iron deficiency has been demonstrated to significantly alter cell-mediated immune functions in children as well as in pregnant women. Circulating T-cell number and in vitro proliferative responses to mitogenic stimuli were found to be significantly impaired in children having iron deficiency and anemia. These effects, however, were reversible with adequate iron repletion. Recent studies demonstrate lack of interleukin-2 (IL-2) production with a predominant interleukin-4 (IL-4) mRNA expression by in vitro mitogen/antigen stimulated lymphocytes obtained from anemic children, suggesting polarization of T-cell subsets towards Th2 population. Sipahi et al. observed decreasing IL-2 and IL-6 concentrations in the serum of iron-deficient children." Bhaskaram 2002, S43.

with malaria.[20] Although observational studies are often less effective than experimental studies for supporting cause-and-effect conclusions due to their higher risk of confounding, it is difficult to imagine how confounding could account for these findings. Typically, a child with more favorable micronutrient status might also have other protective traits, such as a household with higher income, a broadly more nutritious diet, and lower exposure to infectious diseases. Yet this cannot explain the inverse association between iron status and malaria risk since a *less favorable* iron status is associated with lower malaria risk.

Impact of iron supplementation on risk of malaria infection and all-cause mortality

GiveWell's cost-effectiveness analysis for the Evidence Action Beta intervention currently assumes, based on data from the Cochrane meta-analysis Neuberger et al. 2016,[21] that iron/folic acid supplementation increases the risk of dying from malaria by 16 percent. The relevant figure in Neuberger et al. 2016 refers to the risk of malaria incidence, specifically in areas without access to malaria prevention and management services (the authors judged this evidence to be low quality).[22]

Neuberger et al. 2016 provides other relevant estimates:

1. In areas with malaria prevention and management services, iron supplementation reduces the risk of clinical malaria. Relative risk of 0.91 (95 percent confidence interval 0.84 to 0.97). The authors judged this evidence to be low quality.[23]
2. Overall, iron supplementation does not cause an excess of clinical malaria. Relative risk of 0.93 (95 percent confidence interval 0.87 to 1.00). The authors judged this evidence to be high quality.[24]
3. Iron supplementation does not increase mortality risk in malaria-endemic regions. Risk difference of 0.00 (95 percent confidence interval 0.0 to 0.01).[25]
4. Iron and folic acid supplementation does not increase mortality risk in malaria-endemic regions. Risk difference of 0.00 (95 percent confidence interval 0.0 to 0.01).[26]

Since we do not currently know whether children will be located in regions with malaria prevention and management services, it may be preferable to use the pooled estimate (#2).

---

[20] Clark et al. 2014; Sangare et al. 2014.
[21] This is the most recent Cochrane meta-analysis on this topic.
[22] "In areas where there are prevention and management services for malaria, iron (with or without folic acid) may reduce clinical malaria (RR 0.91, 95% CI 0.84 to 0.97; seven trials, 5586 participants, low quality evidence), while in areas where such services are unavailable, iron (with or without folic acid) may increase the incidence of malaria, although the lower CIs indicate no difference (RR 1.16, 95% CI 1.02 to 1.31; nine trials, 19,086 participants, low quality evidence)." Neuberger et al. 2016, abstract.
[23] "In areas where there are prevention and management services for malaria, iron (with or without folic acid) may reduce clinical malaria (RR 0.91, 95% CI 0.84 to 0.97; seven trials, 5586 participants, low quality evidence)." Neuberger et al. 2016, abstract.
[24] Neuberger et al. 2016, abstract.
[25] Neuberger et al. 2016, analysis 1.5, pg. 84-85.
[26] Neuberger et al. 2016, analysis 2.3, pg. 105.

This estimate suggests that iron supplementation does not increase the risk of clinical malaria, and may be slightly protective. We would require further investigation to determine if malaria prevention and management services are present in the relevant regions.

Here is a summary of reasons why it may be preferable to discount subgroup analyses (from trials grouped according to the availability of malaria services), relative to the overall pooled estimate:

- The pooled estimate (#2) is based on a higher-quality evidence base.
- Subgroup analyses are generally less reliable than pooled analyses.
- While both subgroup findings are statistically significant, their confidence intervals nearly include one and nearly overlap, suggesting that they border on nonsignificance.
- It seems somewhat implausible that iron would have opposite effects on malaria risk in areas with vs. without malaria prevention and treatment services.

Although estimates 3 and 4 are not specific to malaria mortality, they suggest that iron supplements with or without folic acid do not substantially increase all-cause mortality in malaria-endemic regions. The 95 percent confidence intervals imply that iron supplements are unlikely to increase mortality risk by more than one percent. They are therefore generally consistent with estimate #2. However, the small number of deaths prevents strong conclusions.[27]

It is also worthwhile to note that this analysis excludes Sazawal et al. 2006,[28] a large RCT of iron and folic acid supplementation in a malaria-endemic region that reported greater hospitalization or mortality in the supplemented group. This study was excluded because it did not isolate the effects of iron from those of folic acid. Folic acid has the potential to interfere with antimalarial medications, complicating interpretation of the findings, yet the results are nevertheless relevant to supplementation interventions involving both iron and folic acid in areas with malaria treatment services. It is worthwhile to note that a subgroup analysis of Sazawal et al. 2006, Sazawal et al. 2014,[29] did not identify an association between folic acid supplementation, iron supplementation, and antimalarial treatment outcome in this context. This RCT used a relatively low dose of folic acid.

The most reliable overall conclusion of this meta-analysis may be that iron supplementation does not increase the risk of being diagnosed with clinical malaria, although it is debatable which estimate is most appropriate for areas without malaria treatment and prevention services. These findings provide some reassurance that iron supplementation does not increase all-cause mortality in malaria-endemic areas, although the evidence underlying this conclusion is not strong. We have not considered evidence beyond this meta-analysis, nor have we examined the

[27] 44 in the iron groups; 38 in the control groups; 21 studies total. Neuberger et al. 2016, analysis 1.5, pg. 84-85.
[28] Sazawal et al. 2006.
[29] Sazawal et al. 2014.

primary studies underlying this meta-analysis, so these conclusions remain somewhat uncertain.

Impact of iron fortification on risk of malaria infection and mortality

Fortification typically involves a lower dose of iron than supplementation, raising the possibility that it has a different impact on malaria risk. We have not identified meta-analyses of the impact of iron fortification on malaria risk. In a medium-depth literature search in PubMed using the search terms "iron fortif* infection randomized" and "iron fortif* malaria randomized", we identified five RCTs that tested the impact of iron fortification on malaria risk:

- Rohner et al. 2010 conducted a 6-month RCT in 6-to-14-year-old schoolchildren in Côte d'Ivoire. Researchers randomized 591 children to eight groups offering iron-fortified biscuits (20 mg iron/day) vs. placebo, intermittent preventive treatment of malaria vs. placebo, and deworming vs. placebo (2 x 2 x 2 factorial design).[30] Iron fortification did not significantly alter iron status or malaria risk.[31,32]
- Zlotkin et al. 2013 conducted a 6-month cluster-randomized controlled trial in children 6 to 35 months old in Ghana. The trial included a total of 1,958 children in two groups. Children in one group received a multiple-micronutrient powder with 12.5 mg of iron per day, while those in a control group received the same powder without iron. Parents added the powder to the children's food. We were unable to determine the overall effect of iron supplementation on iron status from the information provided in the manuscript. The incidence of malaria was significantly lower in the iron-supplemented group compared with control (relative risk of 0.87; 95 percent confidence interval of 0.79 - 0.97).[33] This difference became marginally nonsignificant after adjusting for baseline iron deficiency and anemia status in secondary analyses.[34]
- Barth-Jaeggi et al. 2015 conducted a 12-month RCT in 6-month-old Kenyan infants. Researchers randomized 287 infants into two groups, one receiving daily corn porridge fortified with a micronutrient powder containing 2.5 mg iron, and the control group receiving the same corn porridge and micronutrient powder without iron. Iron fortification did not significantly alter iron status or malaria risk.[35]

---

[30] Rohner et al. 2010, table 1.
[31] "Iron fortification did not improve iron status, IPT of malaria did not affect malaria burden, and neither had an impact on anemia prevalence." Rohner et al. 2010, abstract.
[32] Rohner et al. 2010, table 4.
[33] "In intention-to-treat analyses, malaria incidence overall was significantly lower in the iron group compared with the no iron group (76.1 and 86.1 episodes/100 child-years, respectively; risk ratio (RR), 0.87 [95% CI, 0.79-0.97]), and during the intervention period (79.4 and 90.7 episodes/100 child-years, respectively; RR, 0.87 [95% CI, 0.78-0.96])." Zlotkin et al. 2013, abstract.
[34] "In secondary analyses, these differences were no longer statistically significant after adjusting for baseline iron deficiency and anemia status overall (adjusted RR, 0.87; 95% CI, 0.75-1.01) and during the intervention period (adjusted RR, 0.86; 95% CI, 0.74-1.00)." Zlotkin et al. 2013, abstract.
[35] "Over the 1 year, Hb increased and SF decreased in both groups, without significant treatment effects of the iron fortification… In this study, low-dose iron-containing MNP did not improve infant's iron status or

- Jaeggi et al. 2015 conducted two small 6-month RCTs in 6-month-old Kenyan infants. Researchers randomized a total of 115 infants into four groups (two groups per trial). All four groups received daily corn porridge fortified with a micronutrient powder. In addition to the micronutrient powder, one group in the first trial received 2.5 mg iron, one group in the second trial received 12.5 mg iron, while the other two (control) groups did not receive additional iron. The 12.5 mg dose of iron increased multiple markers of iron status, while the 2.5 mg dose had no effect on these markers.[36] Neither dose significantly impacted malaria risk, although the study probably had insufficient statistical power to detect an effect.[37]
- Glinz et al. 2015 conducted a 9-month cluster-randomized controlled trial in children 12-36 months in Côte d'Ivoire, "an area of intense and perennial malaria transmission".[38] Each of five groups contained 124-127 children. Children in one group received a porridge containing 5.8 mg of iron, six days per week, while a control group received their normal diet (among other groups testing intermittent preventive treatment of malaria).[39] Iron fortification reduced the prevalence of iron deficiency, did not significantly impact anemia risk, and did not affect the concentration of malaria parasites in blood.[40,41]
- [added 4/9/19] Lanou et al. 2019 conducted a 12-month cluster-randomized controlled trial in children 6-23 months in a region of Burkina Faso with very high malaria incidence. Researchers randomized 62 villages into two groups (2,233 children at baseline). Mothers in the intervention group received 15 packets per month of multiple micronutrient powders to add to their children's food, each of which contained 10 mg of

---

reduce anaemia prevalence, likely because absorption was inadequate due to the high prevalence of infections and the low-iron dose." Barth-Jaeggi et al. 2015, abstract.

[36] "There was a significant treatment effect of +12.5 mg FeMNP versus −12.5 mg FeMNP on body iron (p=0.001), SF (p=0.004), sTfR (p=0.008), ZPP (p=0.039) and a trend towards an effect on hepcidin-25 (p=0.052, see online supplementary table S3). By contrast, there was no significant treatment effect of +2.5 mg FeMNP versus −2.5 mg FeMNP on any iron status indicator or hepcidin-25." Jaeggi et al. 2015, Pg. 737.

[37] "During the intervention, incidences of treated RTI and malaria did not significantly differ between +FeMNP versus −FeMNP." Jaeggi et al. 2015, Pg. 738.

[38] "A 9-month cluster-randomised, single-blinded, placebo-controlled intervention trial was carried out in children aged 12–36 months in south-central Côte d'Ivoire, an area of intense and perennial malaria transmission." Glinz et al. 2015, abstract.

[39] "The study groups were: group 1: normal diet and IPT-placebo (n = 125); group 2: consumption of porridge, an iron-fortified complementary food (CF) with optimised composition providing 2 mg iron as NaFeEDTA and 3.8 mg iron as ferrous fumarate 6 days per week (CF-FeFum) and IPT-placebo (n = 126); group 3: IPT of malaria at 3-month intervals, using sulfadoxine-pyrimethamine and amodiaquine and no dietary intervention (n = 127); group 4: both CF-FeFum and IPT (n = 124); and group 5: consumption of porridge, an iron-fortified CF with the composition currently on the Ivorian market providing 2 mg iron as NaFeEDTA and 3.8 mg iron as ferric pyrophosphate 6 days per week (CF-FePP) and IPT-placebo (n = 127)." Glinz et al. 2015, abstract.

[40] "At baseline, anaemia (Hb <11.0 g/dl) was 82.1 %. After 9 months, IPT decreased the odds of anaemia (odds ratio [OR], 0.46 [95 % CI 0.23–0.91]; P = 0.023), whereas iron-fortified CF did not (OR, 0.85 [95 % CI 0.43–1.68]; P = 0.68), although ID (plasma ferritin <30 μg/l) was decreased markedly in children receiving iron fortified CF (OR, 0.19 [95 % CI 0.09–0.40]; P < 0.001)." Glinz et al. 2015, abstract.

[41] "In the 2 × 2 factorial analysis, neither intervention significantly affected the P. falciparum prevalence at 6 or 9 months follow-up." Glinz et al. 2015, Pg. 8. Also see table 2.

iron and 14 other micronutrients. The intervention had no impact on hemoglobin levels or malaria risk (relative risk of malaria 0.68; 95% confidence interval 0.37 to 1.26).[42]

Of the five randomized controlled trials we identified that isolated the effects of iron fortification on malaria risk, none report that iron fortification increases risk, and one suggests that it may reduce risk. However, only two of five trials clearly increased iron status, and among those two, one did not impact the prevalence of anemia and the other likely had low statistical power to detect changes in malaria risk. Therefore, these findings are difficult to strongly extrapolate to malaria-endemic settings in which fortification is expected to increase iron status.

We did not identify evidence on the impact of iron fortification on malaria-related mortality.

Impact of iron supplementation and fortification on risk of non-malaria infection

Among non-malaria infections, diarrhea and respiratory tract infections are the most relevant to GiveWell because they are the primary causes of non-malaria infectious disease mortality in low-income settings[43]. However, we considered all available data on the impact of iron supplementation and fortification on the risk of non-malaria infections.

Impact of iron supplementation on risk of non-malaria infection

In a medium-depth literature search, we identified three meta-analyses of RCTs examining the impact of iron supplementation on the risk of non-malaria infection.

- Gera and Sachdev 2002 included 28 iron supplementation and fortification RCTs representing 7,892 children. The primary outcomes related to infection risk. It did not exclude RCTs conducted in higher-income settings. Iron fortification/supplementation did not significantly affect the risk of acquiring any infection (relative risk of 1.02; 95 percent confidence interval 0.96 to 1.08). However, in 17 trials it did increase the risk of developing diarrhea by 11 percent (relative risk of 1.11; 95 percent confidence interval 1.01 to 1.23). In eight trials, it did not significantly affect the risk of lower respiratory tract infection (relative risk of 0.97; 95 percent confidence interval 0.83 to 1.23).[44] In secondary analyses, whether studies came from “developed” vs. “Asian or African” countries did not affect the findings for any infection, nor did whether the study used supplementation or fortification.[45]
- Pasricha et al. 2014 included 35 iron supplementation RCTs representing 42,306 infants 4-23 months old. The primary outcomes related to iron status, growth, and development. It did not exclude RCTs conducted in higher-income settings. Iron supplementation

[42] See table 3 for anemia data and table 6 for malaria data. Lanou et al. 2019.
[43] GBD Compare. HIV and tuberculosis are also major causes of mortality in low-income settings.
[44] Gera and Sachdev 2002, table 4.
[45] Gera and Sachdev 2002, table 6.

reduced the risk of anemia (relative risk of 0.61) and iron deficiency (relative risk of 0.30). In three studies, iron supplementation increased the incidence of vomiting (relative risk of 1.38; 95 percent confidence interval 1.10 to 1.73). In four studies, iron supplementation increased the prevalence of fever (relative risk of 1.16; 95 percent confidence interval 1.02 to 1.31). The data in this study appear to be insufficient to reach conclusions about lower respiratory tract infections.

- Neuberger et al. 2016 included 35 iron supplementation RCTs representing 31,955 children in regions where malaria is endemic. The primary outcomes related to malaria risk. Iron supplementation increased hemoglobin by 0.67 g/dL.[46] In 14 studies, iron supplementation did not impact the likelihood of hospitalization or visiting a clinic (relative risk of 0.99; 95 percent confidence interval 0.94 to 1.04).[47] In six studies, iron supplementation did not impact the risk of fever (relative risk of 1.03; 95 percent confidence interval 0.93 to 1.14).[48] In ten studies, iron supplementation increased the risk of diarrhea (relative risk of 1.15; 95 percent confidence interval 1.06 to 1.26).[49] In eight studies, iron supplementation did not impact the risk of upper respiratory tract infection or pneumonia (relative risk of 0.99; 95 percent confidence interval 0.85 to 1.15).[50]

Overall, meta-analyses suggest that iron supplementation can increase the risk of gastrointestinal illness such as diarrhea and vomiting, yet iron supplementation appears to have little or no effect on the overall rate of illness or on other prevalent categories of non-malaria illness including respiratory tract infections. We have not examined the studies underlying these meta-analyses so these conclusions remain somewhat uncertain.

Impact of iron fortification on risk of non-malaria infection

Fortification typically involves a lower dose of iron than supplementation, raising the possibility that it has a different impact on non-malaria infection risk. We have not identified meta-analyses of the impact of iron fortification on non-malaria infection risk. In a medium-depth literature search in PubMed using the search terms “iron fortif* infection randomized” and “iron fortif* malaria randomized”, we identified five randomized controlled trials (RCTs) that tested the impact of iron fortification on non-malaria infection risk:

- Power et al. 1991 conducted a 9-month RCT in 3-month old infants from “a lower socioeconomic coloured community” in urban South Africa.[51] Researchers randomized 149 infants to two groups, one receiving commercial infant formula containing 8.3 mg of

[46] This is slightly more than half a standard deviation for US adults. See tables 1 and 2 of Lacher et al. 2012.
[47] Neuberger et al. 2016, analysis 1.12, Pg. 92.
[48] Neuberger et al. 2016, analysis 1.18, Pg. 99.
[49] Neuberger et al. 2016, analysis 1.17, Pg. 98.
[50] Neuberger et al. 2016, analysis 1.20, Pg. 101.
[51] Power et al. 1991, Pg. 58.

iron per 100 g, and the other receiving the same infant formula with added iron to 40 mg of iron per 100 g. Iron fortification increased iron status by several measures,[52] but had no significant effect on total infection risk, gastrointestinal infection risk, or respiratory tract infection risk.[53]

- Heresi et al. 1995 conducted a 15-month RCT in newborns in an urban area of Chile. Researchers randomized 1,655 infants to two groups, one receiving powdered cow's milk and the other receiving powdered cow's milk fortified with 15 mg of iron per day. Iron fortification significantly reduced the prevalence of anemia,[54] but had no significant impact on the incidence of diarrhea or respiratory tract infections.[55]
- Zlotkin et al. 2013 conducted a 6-month cluster-randomized controlled trial in children 6 to 35 months old in a malaria-endemic region of Ghana. The trial included a total of 1,958 children in two groups. Children in one group received a multiple-micronutrient powder with 12.5 mg of iron per day, while those in a control group received the same powder without iron. Parents added the powder to the children's food. We were unable to determine the overall effect of iron supplementation on iron status from the information provided in the manuscript. Overall hospital admissions tended to be higher in the iron group, but this was not statistically significant (relative risk of 1.17; 95 percent confidence interval 0.98 to 1.40).[56] When hospitalization data were divided between the five-month intervention period and the one-month postintervention period, the rate of hospital admission in the iron group was higher than control during the intervention period (relative risk of 1.23; 95 percent confidence interval 1.02 to 1.49).[57] The intervention had no significant impact on the risk of pneumonia or diarrhea.[58]
- Barth-Jaeggi et al. 2015 conducted a 12-month RCT in 6-month-old Kenyan infants in a malaria-endemic region. Researchers randomized 287 infants into two groups, one receiving daily corn porridge fortified with a micronutrient powder containing 2.5 mg iron, and the control group receiving the same corn porridge and micronutrient powder without

---

[52] "The formula with the extra iron proved to be safe and, when compared with the control group, the children in the test group had significantly improved iron status as reflected by the proportion of children classed as normal (25 of 61 cf. 44 of 65; p<0.003), and by the mean values of the haemoglobin concentration (11.5 cf. 11.9 g/dl; p=0.04), red cell distribution width (15.5% cf. 14.4%; p=0.0005), red cell zinc protoporphyrin (3.4 cf. 4.0 ug/g Hb; p = 0.04) and ferritin (29 cf. 17.3 ug/l; p = 0.004)." Power et al. 1991, abstract.

[53] Power et al. 1991, table 3.

[54] "The efficacy of the applied iron fortification was established by determining the incidence of iron deficiency when infants reached 9 and 15 months of age. Iron deficiency anemia was defined as hemoglobin level <llOg/l. At 9 and 15 months, the incidence of anemia was 11.8 vs. 32.5% and 5.5 vs. 29.9% for fortified compared to non-fortified groups respectively, (x2, p < 0.001)." Heresi et al. 1995, Pg. 386.

[55] "Episodes (mean +/- SD) of diarrhea/infant/year were 1.06 +/- 1.29, 1.14 +/- 1.37, and 0.82 +/- 1.04 for the fortified, non-fortified and breast-fed groups, respectively; the fortified and non-fortified bottle-fed groups had a very similar incidence of respiratory illness; 2.66 +/- 2.07 and 2.74 +/- 2.24 episodes/infant/year, respectively." Heresi et al. 1995, abstract.

[56] Zlotkin et al. 2013, table 3.

[57] Zlotkin et al. 2013, table 3.

[58] Zlotkin et al. 2013, table 3.

iron. Iron fortification did not significantly alter iron status.[59] Mothers in the iron group reported that their children spent more days with a cough, and more days with labored breathing (7.4 vs. 6.4; P = 0.003; 2.2 vs. 1.5; P = 0.0002, respectively).[60] The researchers state that "days spent with diarrhoea, flu, bloody or mucus-containing stool, and any other illness did not differ between the two treatment groups."[61] Given the number of hypothesis tests in this study and the lack of correction for multiple comparisons, it is possible that the results for cough and labored breathing are false positives.

- Jaeggi et al. 2015 conducted two small 6-month RCTs in 6-month-old Kenyan infants in a malaria-endemic region. Researchers randomized a total of 115 infants into four groups (two groups per trial). All four groups received daily corn porridge fortified with a micronutrient powder. In addition to the micronutrient powder, one group in the first trial received 2.5 mg iron, one group in the second trial received 12.5 mg iron, while the other two (control) groups did not receive additional iron. The 12.5 mg dose of iron increased multiple markers of iron status, while the 2.5 mg dose had no effect on these markers.[62] There was a trend toward a greater incidence of treated episodes of diarrhea in the group receiving 12.5 mg iron relative to its control group, and although the difference was large, it did not reach statistical significance (27.3% vs. 8.3%, p = 0.092).[63] The incidence of respiratory tract infection did not differ significantly between groups.[64] This study probably did not have sufficient statistical power to detect differences in disease incidence, suggesting that these findings are not very informative.
- [added 4/9/19] Lanou et al. 2019 conducted a 12-month cluster-randomized controlled trial in children 6-23 months in a region of Burkina Faso with very high malaria incidence. Researchers randomized 62 villages into two groups (2,233 children at baseline). Mothers in the intervention group received 15 packets per month of multiple micronutrient powders to add to their children's food, each of which contained 10 mg of iron and 14 other micronutrients. The intervention had no significant impact on

---

[59] "Over the 1 year, Hb increased and SF decreased in both groups, without significant treatment effects of the iron fortification… In this study, low-dose iron-containing MNP did not improve infant's iron status or reduce anaemia prevalence, likely because absorption was inadequate due to the high prevalence of infections and the low-iron dose." Barth-Jaeggi et al. 2015, abstract.

[60] "During the 1-year intervention, mothers from infants in the MNP + Fe group reported more days spent with cough (7.4 vs. 6.4; P = 0.003) and dyspnoea (2.2vs. 1.5; P = 0.0002). Days spent with diarrhoea, flu, bloody or mucus-containing stool, and any other illness did not differ between the two treatment groups." Barth-Jaeggi et al. 2015, Pg. 156.

[61] Barth-Jaeggi et al. 2015, Pg. 156.

[62] "There was a significant treatment effect of +12.5 mg FeMNP versus −12.5 mg FeMNP on body iron (p=0.001), SF (p=0.004), sTfR (p=0.008), ZPP (p=0.039) and a trend towards an effect on hepcidin-25 (p=0.052, see online supplementary table S3). By contrast, there was no significant treatment effect of +2.5 mg FeMNP versus −2.5 mg FeMNP on any iron status indicator or hepcidin-25." Jaeggi et al. 2015, Pg. 737.

[63] "However, there was a trend towards a greater incidence of treated episodes of diarrhoea in +12.5 mg FeMNP versus −12.5 mg FeMNP: 27.3% (n=6/22) versus 8.3% (n=2/24, p=0.092)." Jaeggi et al. 2015, Pg. 738.

[64] "During the intervention, incidences of treated [respiratory tract infection] and malaria did not significantly differ between +FeMNP versus −FeMNP." Jaeggi et al. 2015, Pg. 738.

> hemoglobin levels or the risk of diarrhea (relative risk 1.68; 95% confidence interval 0.94 to 3.08), cough (relative risk 2.21; 95% confidence interval 0.96 to 5.13), or fever (relative risk 1.20; 95% confidence interval 0.82 to 1.77),[65] although diarrhea and cough risk tended to be higher.

RCTs provide limited and inconsistent evidence that iron fortification increases infection risk. Zlotkin et al. 2013, which was conducted in a malaria-endemic region, reported higher overall hospitalization rates in iron-fortified children during but not immediately after the intervention. Some of these hospitalization events were presumably due to malaria. Barth-Jaeggi et al. 2015 reported a higher incidence of respiratory tract infections among iron-fortified children. The other four studies did not replicate these findings. No study reported a significantly increased risk of gastrointestinal illness, which was the primary concern arising from supplementation studies, although two did report trends in that direction.

The evidence base for fortification is considerably smaller than that for supplementation, suggesting that it may be more uncertain, and supplementation only had an impact on the risk of gastrointestinal illness. Given the lower doses of iron used in fortification, it seems unlikely that fortification would cause adverse effects not observed for supplementation. Combined with the lack of confirmation by other fortification studies, this leads us to favor the view that the adverse effects identified in Zlotkin et al. 2013 and Barth-Jaeggi et al. 2015 may be idiosyncratic to those studies.[66] Overall, we do not believe current evidence provides compelling reasons to believe that iron fortification increases the risk of non-malaria infections.

[65] See table 3 for anemia data and table 6 for illness data. Lanou et al. 2019.
[66] For example, false positive findings that result from performing many hypothesis tests without correcting for multiple comparisons.