Review of GiveWell Iron CEA

June 17, 2024

Reina Engle-Stone

Congratulations on putting together a very thoughtful model and report. I appreciate that it is thorough and well-documented. Below are brief responses to the questions posed by email (in blue), and further comments are organized into sections below.

Questions:

- Do our estimates of the effect of iron supplementation and fortification programs on anemia in real-world settings (25% reduction for people reached by fortification programs and 40% reduction for supplementation programs) seem plausible to you?
    - Does the magnitude of adjustments we are using that we expect to impact the effectiveness of iron fortification programs (e.g., inflammation in response to infection) seem reasonable?
    - Are there other important factors affecting the effectiveness of iron fortification and supplementation programs that we aren't currently adjusting for?

  In short, I think the general direction of each adjustment is reasonable. The starting estimate of 50% reduction for supplementation seems optimistic. Suggest to do some sensitivity analyses around this; one would be to start with the 39% reduction from the Andersen paper (see comments below). In modeling multiple micronutrient supplements in pregnancy, our group also found that accounting for adherence can make a big difference to cost-effectiveness estimates and I would guess the same is true here.

  For fortification, as in my comments below I think it is important to have a good understanding of the distribution of food vehicle intake and how this overlaps with the distribution of deficiency. An example would be our earlier work in Cameroon (Engle-Stone, J Nutr, 2009), and more recent work with proxy data (Adams, Ann NYAS, 2024). It might be possible to do some sensitivity analyses now, and some primary data collection could potentially be very useful to understand program impact.

  That said, there is much less uncertainty in the impacts on anemia compared to other outcomes, such as income. Would the CEA still be considered favorable if there were no impact on income?

- Are there any important benefits of iron supplementation and fortification programs that you think we aren't currently accounting for?

  Is the scope necessarily limited to iron? Co-fortification with multiple micronutrients is relatively straightforward and this opens the door to estimating potential benefits such as neural tube defects averted (folic acid) and lives saved among children (vitamin A, zinc).
  For iron there is some evidence on cognitive impacts among adults (eg trials on biofortified beans: Wenger J Nutr 2019; Murray-Kolb J Nutr 2017) but I have not reviewed these through the lens of use in modeling...

- Do you agree with the major sources of uncertainty we highlight in the report? Are there any others you would emphasize?
  I think the report nicely highlights some key sources of uncertainty. What I would emphasize more are the gaps related to 'scaling' from trials to programs: 1) adherence to supplement use, and 2) similarly, fortified food consumption patterns, in the case of fortified foods.

- Are there ways you think we could reduce our sources of uncertainty (including through funding additional research)?
  For proposed or funded programs, you could address this through pilot research and/or monitoring/implementation research. A relatively small study with high quality data collection could help to address some of the assumptions around what people are consuming, how much, how often. This might give some confidence in how well the program is working, and/or suggest avenues to increase the impact.

- Does our assumption that anemia Years Lived with Disability (YLDs) would decline by the same proportion as anemia prevalence seem reasonable to you?
  This seems reasonable to me as a simplifying assumption. There are probably empirical data to answer this but I haven't looked at this. I suppose this assumes that the whole Hb distribution is shifted by supplementation and fortification, which would be most likely to be true if 1) prevalence of anemia is relatively high (and mostly attributable to iron deficiency), and 2) most of the population has access to the intervention.

- The report and cost-effectiveness analysis focus on India, but we may also consider supporting iron fortification or supplementation programs in sub-Saharan Africa in the future. Do you have a view on the likelihood that iron fortification or supplementation programs could cause harm in populations where malaria is prevalent? What else would you look for to be different across settings that could impact whether iron programs could cause harm?

  I think this needs to be better studied for supplementation and especially for fortification programs. In my view there is the potential for harm but the benefits need to be weighed against the risks. Where the need has been documented (with biomarkers, in the case of iron) I think it's reasonable to go ahead while following WHO guidance for concurrent implementation of iron supplementation and malaria control programs. Note also some of the concerns about iron are related to gut pathogens and diarrhea risk, and not just malaria. I would also like to add that I agree with other comments that the risks from fortification are likely lower than those from supplementation.

Other comments

Terminology – dietary iron deficiency

The term "dietary iron deficiency" is specific to GBD and not really used in nutrition literature. Instead we talk about iron deficiency (measured using iron biomarkers) or inadequate iron intake (based on dietary assessment). I'm wondering if you feel that is important to keep this term for consistency with GBD or if you might consider alternatives for your model. GBD estimates of "dietary iron deficiency"

could be used as a proxy for deficiency but they may not agree with primary data on iron status (see Hess et al). It would be more reliable to pull data on dietary intake or deficiency from primary research if available.

Effect of iron supplementation on Hb and anemia

The meta-analysis by Low et al (2013) is used as a starting point for the effect of iron supplementation on anemia. In the Low et al paper, they found that the overall effect was a 50% reduction in anemia (0.50 [0.39 to 0.64], although the forest plot says 0.47 (0.34, 0.66); unfortunately not stratified by baseline anemia or impact on iron-deficiency anemia, IDA).

The newer Andersen paper provides a bit more detail, with estimates for both anemia (RR 0.61 (0.55 to 0.67)) and iron deficiency anemia (RR 0.20 (0.13 to 0.31)).

The GW model adjusts the overall impact of iron on anemia (among all individuals) based on estimates of 'dietary iron deficiency' in the target population vs the countries where the iron supplementation trials were done. In principle it makes sense to adjust so that populations with more IDA benefit more, and vice versa. Concerns are 1) use of the overall effect vs the effect specifically among individuals with anemia, and 2) use of GBD estimates for context-specific adjustment.

An alternative way to adapt your model to other populations is to use the effect size for the intervention impact on the population with anemia (or % iron deficiency anemia, ie both anemia and iron deficiency), and then apply this to the context-specific % of the population with anemia (or iron deficiency anemia). You could look at how the Lives Saved Tool estimates changes in anemia during pregnancy (https://listvisualizer.org/; https://pubmed.ncbi.nlm.nih.gov/28904114/), though the current version uses Food Balance Sheets (national food supply data) to estimate the at-risk population, which is probably not a good proxy for iron deficiency prevalence.

In terms of data sources, I suggest looking at other primary literature to estimate % of anemia that is due to iron deficiency (defined based on biomarkers). First, because of the way GBD estimates 'dietary iron deficiency', but also because it's not clear how the national estimates map to the trial participants. At the very least you could check the validity of the iron deficiency adjustment by comparing the GBD adjustment (line 20 of the Iron supplementation CEA) with an adjustment based on deficiency measured using biomarkers for selected countries.

For India, this survey was just published this year:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10796069/

Among children 1-5 years they found a prevalence of anemia of 40.5%. If I am reading this table correctly, it looks like 66.9% of anemia cases also had iron deficiency (https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30094-8/abstract). This earlier paper also presents the data for 5-9 y and adolescents:
https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30094-8/abstract

Based on those results you might consider stratifying the model by preschool vs school-age children.

Note that WHO recently released new hemoglobin cutoffs. I don't think these will affect your analysis much, if at all. https://www.who.int/publications/i/item/9789240088542

Inflammation adjustment

I appreciate that you are trying to take this into account, but I think it's really hard to put a number on this. It seems reasonable to incorporate a small downward adjustment to be conservative.

There are some studies on iron absorption and inflammation that I believe could be used to estimate the % reduction during that study period, but I'm not sure that is worth pursuing since at the population level it would depend on the % of days affected.

Related, iron status is also an important determinant of iron absorption, and one that could be estimated (at least theoretically, by estimating effects among those with vs without iron deficiency at baseline) though I'm not sure offhand if there are estimates on this that could be readily pulled from the literature.

Iron absorption

It's very good that you are considering differences in iron absorption by fortificant compound and the supplemental dose.

One big piece I don't see is adherence. I think it's fair to argue that adherence could be better for a weekly supplement compared to daily, but it's still likely to be lower in a program context compared to a trial. By adding this parameter to the model you could also do some sensitivity analyses around what minimum adherence you would need for this to still be a cost-effective investment (and consider how investments to improve adherence might impact cost effectiveness).

Excel model:

1. I see the age of program beneficiaries (lines 21-22) is pulled from GBD. Would this be replaced with a more specific source depending on the program context modeled?

Iron fortification

Regarding the Field 2021 meta-analysis – one concern with interpretation is that it combines different iron fortificants. In particular, the Nestel 2004 data are heavily weighted and use electrolytic or reduced iron which does not have high bioavailabiity. Seems worth investigating what the effect would be if this study were excluded.

Did you consider the Keats 2019 meta-analysis?

Consider separating PSC and SAC in the model as the effects could be different based on age-specific food intake and iron requirements.

I have the same comment as for iron supplements above regarding use of GBD data to adjust for % of anemia attributed to iron deficiency. Suggest to replace with biomarker data if possible, or at least test this where possible.

Bioavailability

It is not clear from this version of the spreadsheet how the duration of the study is taken into account when summarizing the results and relating them to a program context.

Line 31 on the CEA sheet lists 50% instead of 22% - is that an error?

As noted above, for adjustment for effectiveness at scale, ideally the model could account for who is consuming the product and how much.