

# A conversation with Dr. Mical Paul, July 13, 2017

## Participants

- Dr. Mical Paul, MD – Associate Professor, Technion-Israel Institute of Technology
- Josh Rosenberg – Senior Research Analyst, GiveWell
- Rossa O’Keeffe-O’Donovan – Research Consultant, GiveWell

**Note:** These notes were compiled by GiveWell and give an overview of the major points made by Dr. Paul.

## Summary

GiveWell spoke with Dr. Paul as part of its investigation into the evidence base for iron and folic acid supplementation and fortification. The conversation focused on the evidence about the likely effect of fortification of food with iron and folic acid on malaria.

## Key points

- Dr. Paul and her coauthors (Ami Neuberger, Joseph Okebe, and Dafna Yahav) conducted a meta-analysis, published in the Cochrane database of systematic reviews ([http://www.cochrane.org/CD006589/INFECTN\\_iron-supplements-children-living-malaria-endemic-countries](http://www.cochrane.org/CD006589/INFECTN_iron-supplements-children-living-malaria-endemic-countries)), which concluded that iron supplementation does not adversely affect children living in malaria-endemic areas as long as malaria management services are available. In a sub-analysis, it concluded that “In areas where there are prevention and management services for malaria, iron (with or without folic acid) may reduce clinical malaria (RR [risk ratio] 0.91, 95% CI [confidence interval] 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).”
- GiveWell asked Dr. Paul about the quality of malaria prevention and management services in sub-Saharan Africa (where many charities that support iron and folic acid fortification work) in comparison with the prevention and management services that were provided as part of studies included in the meta-analysis. Dr. Paul does not have a strong sense of how services in sub-Saharan Africa typically compare to the services offered during the studies; this was not a focus of the systematic review.
- Dr. Paul believes that it is reasonable to be concerned that iron fortification could increase risk of malaria in regions with high malaria burden and weak malaria prevention and management services. However, these risks should be weighed against the likely benefits. Regarding daily oral iron supplementation, the World Health Organization (WHO) guidelines suggest that, “In malaria-endemic areas, the provision of iron supplementation in

infants and children should be done in conjunction with public health measures to prevent, diagnose and treat malaria (strong recommendation, high quality of evidence).”

([http://who.int/nutrition/publications/micronutrients/guidelines/summary\\_daily\\_iron\\_supp\\_children.pdf](http://who.int/nutrition/publications/micronutrients/guidelines/summary_daily_iron_supp_children.pdf))

- When comparing iron fortification to iron supplementation, it is reasonable to expect a priori that fortification would have weaker effects than supplementation (both in terms of benefits and potential negative effects). Dr. Paul believes that a dose-response analysis could be helpful for estimating the magnitude of the effect of fortification relative to supplementation. However, she noted that such an analysis might be difficult because one would need to account for the dose size relative to the weight of the children being treated (measured in, e.g., milligrams of iron per kilogram of weight per day), and some of the studies cited in the Cochrane review did not include information on the weight of treated children. In comparing longer-term, continuous fortification programs against shorter-term supplementation programs, she believes that the total (cumulative) dose of iron over time is most relevant when considering the potential effects of iron on malaria risk, since individuals are exposed to the malaria parasite continuously.
- The initial trial that found that iron supplementation may increase risk of malaria (Sazawal 2006<sup>1</sup>) was conducted on Pemba Island, Tanzania, a region with essentially no malaria prevention or management services at the time of the study.
- GiveWell asked Dr. Paul whether folic acid supplementation or fortification may increase risk of malaria incidence apart from effects that it may have on reducing the effectiveness of some malaria treatments. Dr. Paul believes that it is not biologically plausible that folic acid could increase malaria incidence through mechanisms other than affecting malaria treatments. There is no biological pathway that suggests this is a risk.
- GiveWell asked Dr. Paul about the potential mechanism by which iron supplementation could decrease malaria risk (in areas where there are adequate malaria prevention and management services). Dr. Paul said that there is not a clear biological mechanism for this effect. It may be that iron supplementation could generally improve health or immune system functioning in a way that reduces risk from malaria, but the particular mechanism has not been well studied.

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<sup>1</sup> Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A, et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomized, placebo-controlled trial. *Lancet* 2006;**367** (9505):133–43.

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