

## **International Union of Nutrition Sciences/ Micronutrient Forum/ NIH Joint Taskforce: Risk Benefit analysis of Iron Supplementation in low-income settings.**

### **Team Members**

Dr Sant-Rayn Pasricha (University of Oxford)

Dr Fayrouz Ashour (NIH)

Dr Parminder Suchdev (CDC)

Dr Laura Murray-Kolb (The Pennsylvania State University/ Johns Hopkins University)

### *Collaborators*

Professor Sue Horton (Health Economist, University of Waterloo)

### *Other skills needed (collaborator or team member):*

Expert in risk-benefit analysis

### **Background**

Anaemia affects 496 million non-pregnant women, 32 million pregnant women and 273 million pre-school children worldwide, especially in low and middle-income settings. Approximately half of this burden has been considered amenable to restitution of iron stores, although this proportion is smaller in malaria endemic settings. Putative effects of iron deficiency anaemia in children include impairment in cognitive development, while in women iron deficiency anaemia is considered to cause fatigue, impaired exercise performance and reduced economic productivity. In pregnancy, anaemia is associated with reduced birthweight. Public health strategies to reconstitute iron stores include distribution of iron supplementation (including multiple micronutrient powders in pre-school children), and the World Health Organization recommends universal distribution of these interventions in settings where anaemia is prevalent. However, a critical recent concern has been the safety of iron supplementation to children living in settings where malaria and other infections are endemic, supported by large randomized controlled trials. Other risks, less commonly discussed, include the risk of fatal overdose from iron (especially in children), iron overload from chronic iron ingestion in individuals with a propensity to load iron, and potential impairments from iron on growth in children.

WHO guidelines recommend universal iron supplementation (or iron-containing micronutrient powders) where anaemia is prevalent. These guidelines are based on GRADE-based evaluations of evidence for pre-defined beneficial and harmful outcomes. However, these guidelines do not incorporate risk-benefit or economic analysis for these interventions. While economic analyses of iron supplementation programmes have been developed, these have not generally attempted to incorporate any assessment of the costs of potential harms associated with iron.

Formal assessment of the benefit-risk is required for implementation of new public health policies (for example, by NICE in the UK) and for licensing of new pharmaceuticals (for example, by the FDA in the US, TGA in Australia). Formal risk-benefit analysis can provide policy-makers and countries with a sophisticated quantification of the potential outcomes associated with an iron supplementation programme than is presently available within WHO guidelines. Together with economic analysis, this information can potentially guide programme managers and policy makers when selecting between various health priorities and public health interventions.

### **Taskforce Objectives**

1. To evaluate the benefit-risk of iron supplementation as a public health intervention.

- a. Sensitivities of assessments to age, intervention and context (e.g. malaria endemicity) will be incorporated.
  - b. If possible, an algorithm will be developed enabling re-evaluation of this assessment in different settings, with different interventions, or as evidence changes.
2. To undertake a health economic evaluation of iron supplementation as a public health intervention.
  - a. Sensitivities of assessments to age, intervention and context (e.g. malaria endemicity) will be incorporated.
  - b. If possible, an algorithm will be developed enabling re-evaluation of this assessment in different settings, with different interventions, or as evidence changes.
3. To identify the evidence gaps limiting benefit-risk and health economic analysis of iron supplementation interventions and make specific recommendations concerning the critical work needed.

### **Proposal**

To undertake a formal:

i) risk-benefit and ii) health economic analysis of iron supplementation as a public health strategy for anaemia control.

*Interventions to be considered:*

Initially:

- Iron supplementation (daily or intermittent).
- Multiple micronutrient powders.

Secondarily:

- Central fortification of foods with iron.

*Populations to be specifically considered:*

- Children under 2 years,
- Children under 5 years,
- Non-pregnant women
- Pregnant women.

### **Methodology**

To be developed by the taskforce.

There are several benefit-risk frameworks available. For example, regulators including the US Food and Drug Administration and the European Medicines Authority use various approaches to evaluate and compare benefit and risk when making decisions about drug licensing. Quantitative, semi-quantitative and qualitative methodologies have been developed. Approaches not only compare the probability of benefit or harm associated with the intervention, but also assign weights to these relevant outcomes, enabling the potential impact of these outcomes on the population or individuals to be incorporated into the evaluation.

*Work of the taskforce*

The taskforce will comprise early- to mid-career researchers with expertise in the relevant issues, representing a broad range of disciplines including nutrition sciences, clinical medicine, evidence-based medicine, experimental biology, and cognitive development. Members will be derived from institutions across the US, Europe, Africa and Australia. An additional participant with experience in formal benefit-risk analysis and health economic analysis will be invited to advise the taskforce with the specifics of undertaking the analyses. In addition, the taskforce will call on the mentorship of a

panel of senior academics and experts including Dr Dan Raiten (NIH), Dr Lynnette Neufeld (GAIN) and Professor Andrew Prentice (LSHTM/ MRC Gambia).

Once the team members have been invited and roles have been defined, the taskforce will select the most appropriate benefit-risk and health economic frameworks within which to perform the analyses. The taskforce members will then obtain the relevant evidence both to quantify the effects of iron supplementation on various outcomes, and to assign appropriate weightings to these outcomes. At a meeting to be held in mid-2015, this evidence will be presented and the taskforce will begin to prepare the benefit-risk analyses. In the latter half of 2015, the analyses will be finalized and prepared for publication. Results will also be presented at the Micronutrient Forum meeting in Cancun in 2016.

During the period the taskforce is operating, it is expected the team will convene monthly by teleconference, and will also meet for a three-day face-to-face meeting mid-2015.

### **Timeline**

Mid July 2014: Invite and confirm team

End July 2014: Scope work and define roles

July to September 2014: Select appropriate benefit-risk and cost-benefit analysis strategy.

September 2014 – April 2015: Quantify and define evidence of risks and benefits. Consider weightings for outcomes.

April 2015: Consultation in Washington DC

May 2015 – December 2015: Undertake risk benefit analysis. Quantify costs for cost-benefit analysis

December 2015 – March 2016: Prepare manuscripts for submission.

June 2016: Publication of supplements. Presentation at MNF Cancun.

### **Key Resources needed**

- Access to expertise in risk-benefit analysis.
- Access to expertise in health economic analysis.
- Teleconference facilities (for monthly meetings).
- Resources to support a face-to-face meeting in mid-2015.
- Librarian support for retrieving publications.
- Assistance with dissemination of findings in peer-reviewed journals.
- Assistance with presenting findings at an international meeting.

### **Outputs**

1. Manuscripts for publication in a peer reviewed journal explaining rationale, approach, methodology and results of analyses.
2. Presentation at a session of Micronutrient Forum 2016 in Cancun.