WHO summary on the available evidence for the content of iron in ready-to-use therapeutic foods for treating children with severe wasting

The World Health Organization (WHO) commissioned a systematic evidence review to evaluate whether increasing the content of iron in ready-to-use therapeutic foods (RUTF) (from 10-14 mg/100 g of RUTF as specified in the Joint Statement[1] to a higher amount) is safe and effectively improves outcomes such as blood haemoglobin concentration and recovery from iron-deficiency anaemia in children with severe wasting.

The review question was framed in the PICO (population, intervention, control, and outcomes) format as follows: in children aged 6 months or older with uncomplicated severe wasting, does higher iron content in RUTF compared with the WHO recommended iron content in standard RUTF improve outcomes such as blood haemoglobin concentration, recovery from iron-deficiency anemia?

Thus, the review focused only on the dose of iron in RUTF; other possible interventions, such as iron supplementation or micronutrient powders, that have the potential to correct iron deficiency or treat anaemia in children with severe wasting were not scoped in the review.

Summary of Findings

After a systematic literature search, three eligible trials were identified. These were randomized controlled trials (RCT) conducted in Zambia, the Democratic Republic of Congo, and Malawi (all in Africa Region). In all three RCTs, soya-maize-sorghum-based (non-dairy) RUTF formulations were used with a higher iron content (per 100 g of RUTF) as follows: 52.5 mg (Irena et al., 2015)[2]; 43.8 mg (Bahwere et al, 2016)[3]; and 35.1 mg (Akomo et al., 2019)[4].

Efficacy

Increasing the iron content in RUTF improved blood haemoglobin concentrations and reduced the prevalence of iron deficiency anaemia (IDA), although the overall effect was small for haemoglobin (mean difference 0.31 g/dL, 95% CI: 0.10, 0.52, p = 0.004) (see Annex 1). The effect was larger for IDA (risk ratio 0.39, 95% CI: 0.15, 0.99, p = 0.05), but the confidence intervals were wide (see Annex 2). Thus, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, the overall certainty of the evidence was judged to be low (i.e., the observed effect may be different from the true effect due to serious risk of bias and imprecision). The risk of bias was deemed to be serious because of lack of data for the full set of study participants. The imprecision was deemed to be serious because the confidence interval around the summary estimate was wide and included a null effect for one of the studies (see Annex 4).

[1] WHO, UNSCN, UNICEF. Community-based management of severe acute malnutrition. A joint statement by the World Health Organization, World Food Programme, United Nations Standing Committee on Nutrition, United Nations Children's Fund. Geneva, World Health Organization. 2007.

[2] Irena AH, Bahwere P, Owino VO, Diop EI, Bachmann MO, Mbwili-Muleya C, et al. (2015). Comparison of the effectiveness of a milk-free soy-maize-sorghum-based ready-to-use therapeutic food to standard ready-to-use therapeutic food with 25% milk in nutrition management of severely acutely malnourished Zambian children: an equivalence non-blinded cluster randomised control trial. Matern Child Nutr. 11(Suppl 4):105–19. doi: 10.1111/mcn.12054.

[3] Bahwere P, Balaluka B, Wells JCK, Mbiribindi CN, Sadler K, Akomo P, et al. (2016). Cereals and pulse-based ready-to-use therapeutic food as an alternative to the standard milk- and peanut paste-based formulation for treating severe acute malnutrition: a noninferiority, individually randomized controlled efficacy clinical trial. Am J Clin Nutr. 103(4):1145–61. doi: 10.3945/ ajcn.115.119537.

[4] Akomo P, Bahwere P, Murakami H, et al. Soya, maize and sorghum ready-to-use therapeutic foods are more effective in correcting anaemia and iron deficiency than the standard ready-to-use therapeutic food: randomized controlled trial. *BMC Public Health.* 2019;19(1):806.

Safety

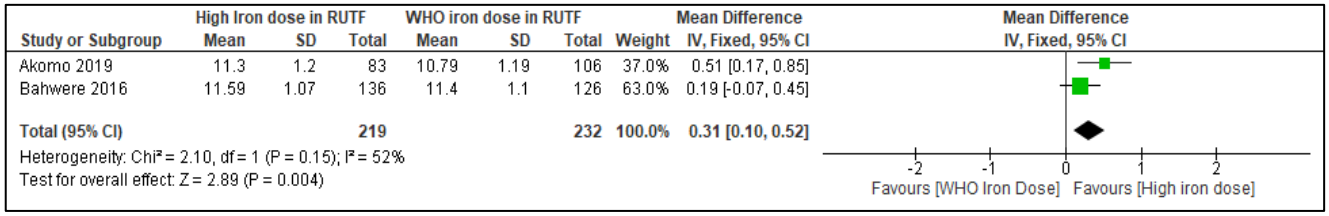
The results showed a potential increase in all-cause mortality for children receiving RUTF with higher iron content compared to those receiving standard RUTF, although this was not statistically significant (risk ratio 1.30, 95% CI: 0.87, 1.95, p = 0.21) (see Annex 3). The lack of significance may be due to the studies being underpowered to detect this outcome. No data were available for malaria, diarrhoea, or respiratory tract infections.

WHO's conclusion:

1. There is rationale to increase the content of iron in RUTF to prevent iron deficiency: children recovering from severe wasting have increased iron needs due to rapid growth rate; the high prevalence of anemia reported at discharge from outpatient therapeutic programmes; and the evidence that provision of RUTFs led to some improvements in haemoglobin status and reduction of anaemia.
2. However, the available evidence is not adequate to determine the optimal content of iron in RUTF. There is need for large randomized controlled trials (RCT) preferably of similar RUTF recipes, but with different doses of iron and designed to demonstrate a dose-response relationship as well as safety.
3. As part of the implementation guidance of the wasting guideline, WHO plans to determine the feasibility of routine checking of haemoglobin status in children recovering from severe wasting; and treating all children diagnosed with anaemia, following the WHO guidelines on treating anaemia in children.

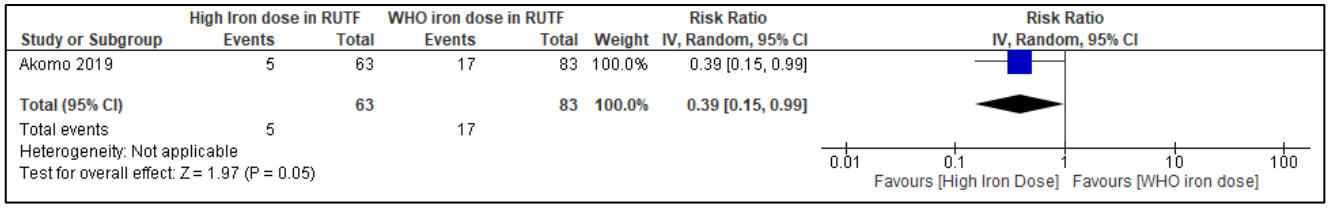
ANNEXES

Annex 1: Effect of RUTF with high iron content compared to RUTF with WHO standard iron content on blood hemoglobin



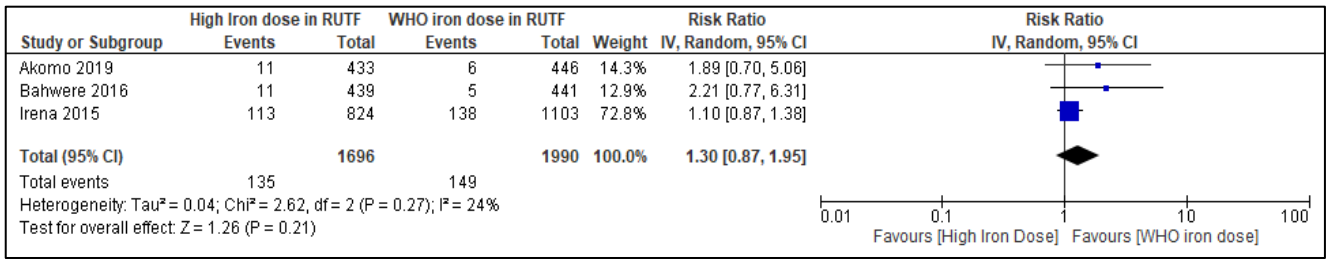
Footnotes: The forest plot shows pooled data from two studies for change in hemoglobin at the end of the study. Both the studies had data available only for a subset of population. The published data from Akomo 2019 was adjusted for altitude and ethnicity however we had access to unadjusted data and we pooled the same to be consistent with data from Bahwere 2016 study. The data from Bahwere 2016 was provided by authors and was not available from the published report. Akomo 2019 has two study groups. We included data from milk free soybean, maize and sorghum (FSMS) and standard formulation prepared from peanut and milk (PM-RUTF).
Abbreviations: RUTF-ready to use therapeutic food; WHO: World Health Organization

Annex 2: Effect of RUTF with high iron content compared to RUTF with WHO standard iron content on iron deficiency anemia



Footnotes: The forest plot shows data from a single study and this study had data available only for a subset of population. Akomo 2019 has two study groups. We included data from milk free soybean, maize and sorghum (FSMS) and standard formulation prepared from peanut and milk (PM-RUTF).
Abbreviations: RUTF-ready to use therapeutic food; WHO: World Health Organization

Annex 3: Effect of RUTF with high iron content compared to RUTF with WHO standard iron content on all-cause mortality



Footnotes: The forest plot shows pooled data from all three included study from this review. Raw values were used and an intention to treat analysis was preferred where available. The pooled results show a potential increase in mortality for children receiving RUTF with high iron content compared to RUTF with standard WHO iron content. Akomo 2019 has two study groups. We included data from milk free soybean, maize and sorghum (FSMS) and standard formulation prepared from peanut and milk (PM-RUTF).
Abbreviations: RUTF-ready to use therapeutic food; WHO: World Health Organization

Annex 4: GRADE Evidence Profile to show the certainty of evidence for the primary outcomes and selected secondary outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High iron content	WHO standard iron content in RUTF	Relative (95% CI)	Absolute (95% CI)	
Blood hemoglobin											
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	219	232	-	MD **0.31 g/dL higher** (0.1 lower to 0.52 higher)	⨁⨁◯◯ Low
Iron deficiency anaemia											
1	randomised trial	serious [c]	not serious	not serious	serious [d]	none	5/63 (7.9%)	17/83 (20.5%)	**RR 0.39** (0.15 to 0.99)	**125 fewer per 1,000** (from 174 fewer to 2 fewer)	⨁⨁◯◯ Low
All-cause mortality											
3	randomised trials	not serious	not serious	not serious	serious [e]	none	135/1696 (8.0%)	149/1990 (7.5%)	**RR 1.30** (0.87 to 1.95)	**22 more per 1,000** (from 10 fewer to 71 more)	⨁⨁⨁◯ Moderate

Explanations

a. Included studies were at high risk of bias for this outcome because the studies reported data for only a subset of the study population.
b. The overall effect seems to be small. Even though the confidence interval of the summary estimate did not include a null effect, the lower limit of the confidence limit was very near to the null effect. The results of the blood hemoglobin were not adjusted for ethnicity and the altitude from both the studies.
c. Included study was at high risk of bias due to lack of data for the full set of study participants.
d. The confidence interval around the summary estimate was wide and included a null effect.
e. The confidence interval around the summary estimate included a null effect with the possibility of a beneficial effect or an increased risk of mortality.