

## Letter to the editor of *Advances in Nutrition*

### Comment on the review and meta-analysis of alternative ready to use therapeutic food formulations containing <50% protein from dairy

From:

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Dear Editor,

The purpose of the systematic review and meta-analysis published by Potani et al. (Potani et al 2021) was to inform the WHO on the efficacy of Ready to Use Therapeutic Foods (RUTF) containing no or less than 50% protein from dairy in the treatment of children with Severe Acute Malnutrition compared with the standard formulation as described by WHO (WHO, WFP 2007). Data from an RCT on the amino acid enhanced plant-based SMS-RUTF, one of the 6 studies included in the Potani meta-analysis, demonstrated that the recipe was highly effective in promoting recovery according to the present WHO and Sphere criteria (Bahwere 2017). Published data also clearly show that the plant-based amino acid enhanced RUTF recipe is more effective at promoting recovery from Iron deficiency and anaemia than the standard WHO accepted milk based recipe with 50% of the protein coming from dairy (Akomo et al. 2019). A subsequent operational pilot of the recipe in a government-run CMAM programme in Malawi also achieved recovery rates of 88.3%, exceeding those recorded in the Bahwere 2017 trial (78%) as well as the Sphere criteria (>75%) and the Ministry of Health target (>85%) (Banda et al. 2021).

The data presented in the systematic review and meta-analysis by Potani et al. on alternative Ready to Use Therapeutic Foods (RUTF) [Potani et al 2021], do not support their conclusion that formulations containing less than 50% of the protein from dairy are less effective in treating uncomplicated Severe Acute Malnutrition (SAM). Pooling of data from fundamentally dissimilar RUTF recipes (as recognised in their study limitations) is flawed and contravenes standard practice for meta-analyses (Crowther, Lim, and Crowther 2010). The author's justification of their flawed methodology, by referring to the non-evidenced based WHO guidelines for RUTF that require that at least 50% of protein should come from dairy, is not scientifically sound and does not support inclusion of such fundamentally different recipes.

Three of the six trials included in the Potani review (Irena et al. 2015; Bahwere et al. 2016; Bahwere 2017) were on recipes made from ingredients that can be grown in countries affected by malnutrition, and were part of a Valid Nutrition, 15 year R & D programme designed to create, a lower cost, non-milk RUTF. The first two studies found that initial formulations were inferior to standard RUTF in terms of recovery rates in children <24 months old but superior in terms of their ability to treat iron deficiency and anaemia (Bahwere et al. 2016; Irena et al. 2015). Additional results also identified several important issues limiting efficacy, in particular the protein quality. Importantly, these trials were part of a developmental process used to identify key nutritional limitations in development of a low cost RUTF. Consequently, data from these trials, together with animal studies on growth and recovery from malnutrition using RUTF recipes fortified with different amino acid mixes (Bahwere et al. 2016; Furuta and Murakami 2018), were used to develop a third, fundamentally different, RUTF enriched with crystalline

amino acids. In a large randomized controlled three arm trial, this new recipe was shown to be non-inferior to standard RUTF with regard to recovery, default, mortality and restoration of essential amino acids (Bahwere et al. 2017; Sato et al. 2018).

Another fundamental flaw in the Potani review is their use of the rate of weight gain as a primary outcome indicator. Differences in the rate of weight gain between the recipes formed the basis for their conclusion that RUTF recipes with <50% of the protein from dairy are less effective. It was also the only indicator used in their cumulative and network meta-analyses. The rate of weight gain as a primary outcome indicator for the treatment of SAM is however not accepted practice. In fact, the Sphere standards governing therapeutic care for SAM specify that the rate of weight gain is a secondary outcome indicator (Sphere Association 2018). This is because the rate of weight gain is not a health outcome in itself and the significance of different rates of weight gain are not known – indeed in some children, very rapid rates of weight gain are undesirable because they are associated with iron deficiency (McCarthy et al. 2018; Thorsdottir et al. 2003). By contrast, the treatment of iron deficiency and iron deficiency anaemia, which receive only passing comment in the Potani review, are life threatening conditions that affect most children with SAM and are better prevented and treated with plant-based RUTFs within the therapeutic care package (Akomo et al. 2019).

A third serious limitation of the Potani study is their cursory examination of the efficacy of the different RUTF recipes in correcting Iron deficiency and treating anaemia. Data from two of the trials included in their meta-analysis clearly shows that the amino acid enhanced plant-based SMS-RUTF recipe is superior to the standard milk-based RUTF in restoration of iron status and treatment of anaemia, and that the benefit to iron status is inversely proportional to the milk content (Akomo et al. 2019). The authors' assertion that the superiority of the plant-based recipes can be explained by differences in the Iron and Vitamin C content of the plant-based recipes are inconsistent with the published data (Akomo & Collins 2020). Iron deficiency and anaemia occur in most cases of Severe Acute Malnutrition and in contrast to the rate of weight gain, a secondary outcome indicator given such prominence in the Potani review, their treatment is an important health outcome in its own right

A final critical omission is the absence of any cost effectiveness analysis. A cost effectiveness analysis formed 1/3 of the original Terms of Reference for the WHO RUTF guideline review, however no analysis was ever undertaken, nor any cost effectiveness data included in the Potani review. The high cost of the RUTF in the face of limited budgets for its procurement, is the most important factor limiting the treatment coverage of Severe Acute Malnutrition to under 20%. Given that the cost of ingredients for the amino acid enhanced plant-based RUTF is >29% lower than those used in the milk based recipe (Collins 2020), the adoption of this new recipe could play a vital role in increasing programme coverage and impact.

A comprehensive meta-analysis of RUTF is urgent because the global coverage of SAM treatment is unacceptably low and new effective lower cost RUTF recipes are urgently needed. However, as a direct consequence of the fundamental flaws and misleading conclusion of the Potani review and the absence of any costs effectiveness analysis, the WHO has now reaffirmed that 50% of the protein in RUTF must come from dairy. This is likely to prevent the use of the much cheaper amino-acid plant-based RUTFs cementing low treatment coverage of SAM for years to come. Adoption of the low-cost amino acid enhanced plant-based RUTF is essential if

treatment coverage is to be increased, treatment integrated with prevention and true competition introduced into the global market for RUTF. Without this, the goals of the Global Action Plan on wasting (Food and Agriculture Organization et al. 2020) will not be attained.

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