

## Original Article

# Soya-maize-sorghum ready-to-use therapeutic food (SMS-RUTF) for the management of severe acute malnutrition among children: A systematic review and meta-analysis

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## Abstract

In managing severe acute malnutrition (SAM) among children, the World Health Organization has endorsed the use of ready-to-use therapeutic foods (RUTF), especially the peanut and milk-based (PM-RUTF), which has been proven for its efficacy. Unfortunately, the distribution of PM-RUTF is challenged by high financial cost and reliance on imports for milk and peanuts. Researchers explore the Soy-Maize-Sorghum (SMS)-RUTF as the alternative, in which the formulation has two types; milk-free soya-maize-sorghum (FSMS)-RUTF and low milk content SMS (MSMS)-RUTF. The aim of this study was to evaluate the efficacy, safety, and acceptance of SMS-RUTFs in the management of SAM among children as compared with PM-RUTF. Eligible studies were searched through PubMed, Scopus, and Embase up to July 14, 2023. Studies reporting the effects of SMS-RUTF, FSMS-RUTF, or MSMS-RUTF intake on SAM with PM-RUTF as the control were considered eligible. The included randomized controlled trials were then assessed for the risk of bias using Cochrane Risk of Bias 2.0. Odds Ratio (OR) and mean difference (MD) were calculated using a random-effects meta-analysis. The analysis focused on investigating the recovery, mortality, weight gain, and hemoglobin levels. Five randomized controlled trials involving a total of 5,513 children were incorporated in this review. Of which, four studies were included in the statistical analysis. Those receiving SMS-RUTF was 0.77 times less likely to recover from SAM as compared to control (95% CI: 0.66–0.90,  $p < 0.01$ ). The SMS-RUTF group had 1 kg lower weight gain as compared to control (95% CI: -1.25–0.75,  $p < 0.01$ ). However, the SMS-RUTF group had significantly higher increase of hemoglobin level than control (MD: 0.80 g/dL [95% CI: 0.68–0.93],  $p < 0.01$ ). Adverse effects were observed similar in both SMS-RUTF and control groups. SMS-RUTF received low acceptance from the participants suspected to be caused by poor packaging. In conclusion, SMS-RUTF is less effective than PM-RUTF in managing SAM among children but can be used to improve anemia as indicated by increased hemoglobin levels.

**Keywords:** RUTF, soy-maize-sorghum, severe acute malnutrition, children, therapeutic food



## Introduction

Childhood malnutrition presents a significant public health challenge, as it is being associated with notable morbidity and mortality [1]. The consequences of malnutrition may manifest in a short or term, leading to issues like illness, death, and disability [2]. In 2022, the United Nations Children's Fund reported that 45.0 million children under 5 years old were wasted, of which 13.7 million were severely wasted [3]. Severe acute malnutrition (SAM) is characterized by a severe deficiency in nutritional intake, leading to significant weight loss, muscle wasting, and stunted growth [4], which encompasses two main forms: severe wasting and nutritional edema [5]. Children affected by the condition often exhibit visible signs of malnutrition, including skeletal prominence and swollen extremities [5].

Despite an 11% decrease in the global prevalence of acute malnutrition among children over the past two decades, this progress is notably modest when compared to the advancements achieved in mitigating other indicators of malnutrition [6]. Early, swift, and precise diagnosis and intervention play an important role in preventing SAM-associated deaths [7,8]. To suppress the number of SAM cases, the World Health Organization (WHO) recommends distribution of ready-to-use therapeutic foods (RUTF) for children aged 6 to 59 months, as part of community-based management of acute malnutrition [9,10]. RUTF is a lipid-based paste comprised of peanut butter, milk powder, oil, sugar, and a vitamin-mineral supplement [11]. The food mirrors the nutritional profile of F100 therapeutic milk and is designed for direct consumption at home, even in less hygienic conditions [12]. The distinctive features of ready-to-use therapeutic food (RUTF) include a comprehensive nutritional composition containing amino acids, vitamins, mineral salts, essential fatty acids, and a high energy density (500–540 kcal/100g). Its long shelf life is suitable for on-site utilization for acute malnutrition programs [13,14]. The widely used RUTF variant, peanut and milk-based RUTF (PM-RUTF), has shown significant success in achieving high recovery rates and minimal fatalities in resource-poor settings [14].

Unfortunately, high milk content in PM-RUTF presents challenges due to increased financial costs and reliance on imports [15]. High expenses associated with shipping and manufacturing the ingredients posing significant challenges in enhancing the availability of RUTFs, especially in economically disadvantaged areas where the ingredients may be difficult to procure [4,16]. Significant endeavors have been undertaken to create RUTF alternatives devoid of milk and peanuts, utilizing locally cultivated and produced crops. Nevertheless, most of these new formulations have proven less efficacious than PM-RUTF in treating SAM in children under the age of 5 [15,17].

Recently developed by Valid Nutrition and Ajinomoto Co. Inc., a more affordable and accessible plant-based RUTF formulation has been created, predominantly using ingredients—such as soya, maize, and sorghum (SMS)—that can be cultivated in most sub-Saharan African countries [13,17]. The nutrient levels in SMS-RUTF exceeded United Nations specifications for RUTF to counterbalance the elevated presence of anti-nutrients found in the plant-based ingredients [14]. Unlike the current PM-RUTF, this formulation excludes milk and peanuts, potentially making it a more cost-effective choice; however, its comparative efficacy as compared to PM-RUTF remains officially undetermined [18]. SMS-RUTF itself can be divided into milk-free soya-maize-sorghum (FSMS)-RUTF and low milk content SMS (MSMS)-RUTF [18]. The aim of this study was to conduct a systematic review dedicated to evaluating the efficacy, safety, and acceptance of SMS-RUTF as a viable alternative compared to the PM-RUTF in the treatment of severe acute malnutrition.

## Methods

### Search and screening strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) guidelines as recommended by Cochrane Collaboration [19]. The search

was conducted by screening the three largest databases (PubMed, EMBASE, and Scopus), along with gray literature sources (Google Scholar and LILACS). The search focused on studies assessing the consumption of SMS-RUTF in the management of SAM among children. The search was performed for studies published up to 14 July 2023. Keywords combinations used in the databases are presented in **Table S1**. The screening and searching processes from the databases were independently carried out by two investigators (C.A.M. and M.R.P.) using Zotero 6.0. The duplicates were removed automatically, and titles and abstracts deemed potentially eligible by either investigator were retrieved for full-text review. Any discrepancies that arose were resolved through consensus involving a third investigator (G.T.).

### **Study eligibility and outcomes of interest**

Studies were selected if they meet the following criteria: (a) recruiting infants and children aged 6 to 59 months diagnosed with severe acute malnutrition who had appetite and did not have medical complications; (b) investigating the effects of RUTF intervention made from soy, maize, and sorghum; (c) the control group employed was given standard RUTF made from peanuts and milk; (d) outcomes included the efficacy, safety, or acceptance; and (e) randomized controlled trials. Studies reporting the efficacy of FSMS-RUTF and MSMS-RUTF were also included. Studies recruiting infants or children diagnosed with moderate acute malnutrition were excluded. Exclusion was also made to studies that administered RUTF containing only one of soy, maize, or sorghum.

Severe acute malnutrition is defined based on WHO criteria; a condition in children with the presentation of oedema of both feet (kwashiorkor with or without severe wasting) or severe wasting (weight-for-height/length  $< -3$  standard deviation or mid-upper arm circumference  $< 115$  mm) [20]. The primary outcomes of interest were the efficacy, safety, and acceptance of SMS-RUTF. Efficacy was defined by the odds of recovery, weight gain, and odds of mortality. Safety was defined by assessing adverse events, while acceptance was defined as consumption of at least 50% of the offered RUTFs. Additionally, secondary outcomes included hemoglobin level expressed in g/dL.

### **Data extraction and quality assessment**

The following data were extracted from each study: (a) first author's name, publication year, and the study location; (b) subject characteristics, consisting of sample size, mean age and proportion of gender, baseline mid upper arm circumference (MUAC), and weight-for-height z score (WHZ); (c) study characteristics, including duration, intervention, as well as comparison; and (d) outcomes. Two reviewers independently (G.T. and M.R.P.) assessed the risk of bias using the Revised Cochrane Risk of Bias tool for randomized controlled trials (RoB 2.0) [21] which consists of five domains, including the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and the overall risk of bias. In each domain, the study was graded as 'low risk', 'high risk', or 'some concerns' Results of RoB 2.0 assessment were presented in traffic light plot.

### **Statistical analysis**

Outcome data presented as median were converted to mean  $\pm$  standard deviation using an free online calculator (<https://math.hkbu.edu.hk>). A meta-analysis was performed on Revman Review Manager 5.4.1 [22]. Odds ratios (OR) and mean difference (MD) were used as the size effect for continuous and dichotomous data, respectively. The estimate also computed 95% confidence intervals (95%CI). A fixed-effect model was employed in the pooled estimate.  $I^2$ -statistics was used to analyze heterogeneity, with cut-off criteria of 0%, 25%, 50%, and 75%, indicating negligible, low, moderate, and high heterogeneity, respectively. The statistical significance level was set at  $p < 0.05$ .

## Results

### Searching results

The PRISMA flow diagram was constructed to illustrate the screening and selection process based on the eligibility criteria set in the study. The flow diagram is presented in **Figure 1**. In the initial search, 304 reports were identified. After eliminating duplicate records and reviewing titles, abstracts, and full texts, five studies were finally included in the present systematic review [4,10,15,17,18].

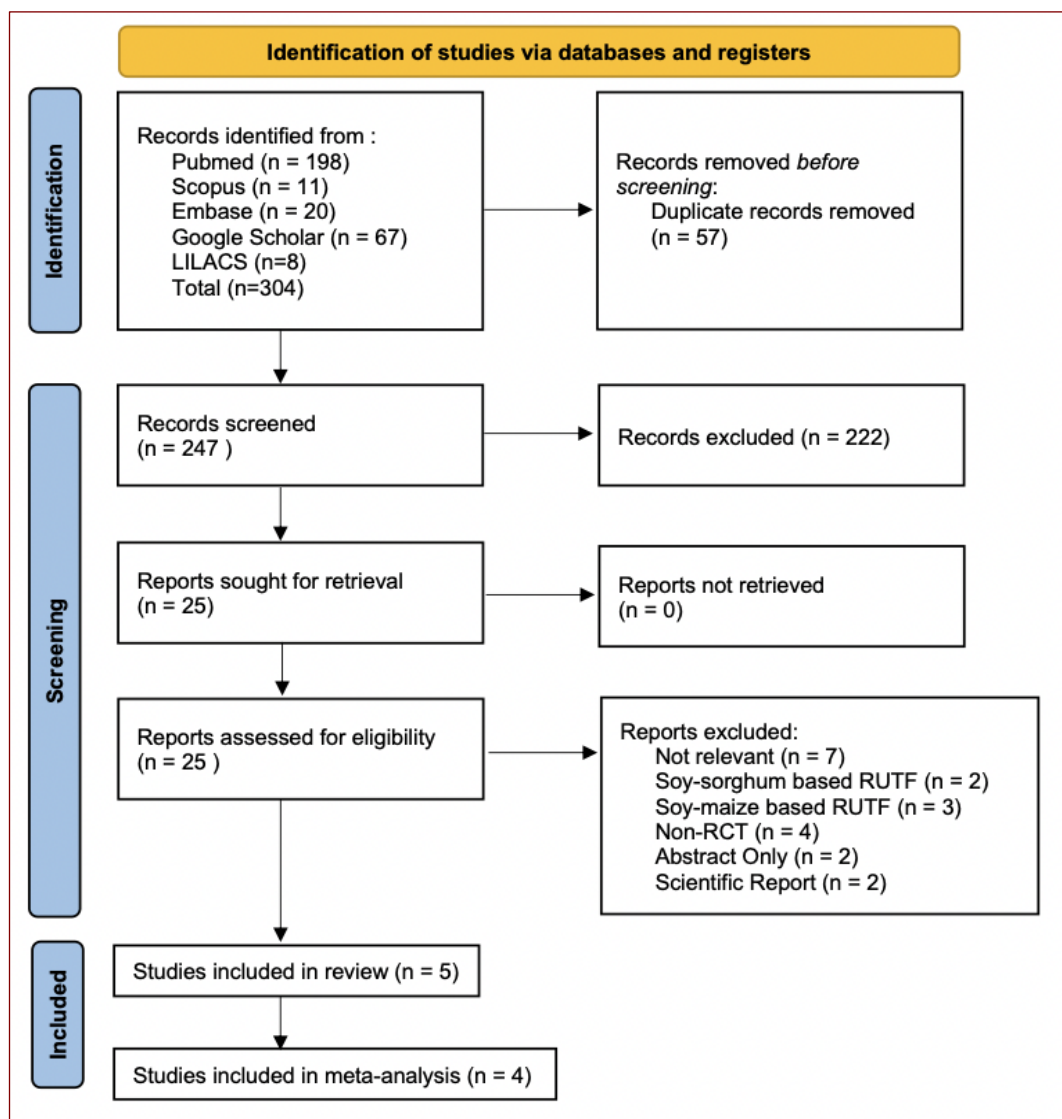


Figure 1. PRISMA flow diagram for screening and selection strategy.

### Study characteristics

Five studies recruiting 5,513 children in total were included in the qualitative analysis [4,10,15,17,18]. The summary of the characteristics and outcomes of the included studies are presented in **Table 1**. All studies were conducted in African countries, namely Malawi, Kongo, and Zambia. The duration of the included studies ranged from 6 to 14 months.

Table 1. Characteristics and outcomes of included studies

| Author, year                      | Country       | Arm  | Characteristics |         |             |            |               | Treatment        |            | Safety                 | Acceptance |
|-----------------------------------|---------------|------|-----------------|---------|-------------|------------|---------------|------------------|------------|------------------------|------------|
|                                   |               |      | n               | M/F     | Age (month) | MUAC       | W-f-L-z score | Duration (month) | RUTF       |                        |            |
| Akomo <i>et al.</i> , 2019 [10]   | Malawi        | ITVN | 243             | 123/120 | NR          | NR         | NR            | 9                | FSMS, SMS  | NR                     | NR         |
|                                   |               | CTRL | 149             | 79/70   | NR          | NR         | NR            | 9                | P          | NR                     | NR         |
| Bahwere <i>et al.</i> , 2016 [4]  | Rep. of Congo | ITVN | 439             | 225/214 | 31.7±13.28  | 11.2±0.87  | -2.31±1.22    | 12               | SMS        | NR                     | low        |
|                                   |               | CTRL | 436             | 201/235 | 34.36±14.67 | 11.2±0.7   | -2.47±1.09    | 12               | P          | NR                     | NR         |
| Bahwere <i>et al.</i> , 2017 [18] | Malawi        | ITVN | 881             | 531/350 | 15.18±12.59 | 11.66±0.43 | -2.34±1.44    | 9                | FSMS, MSMS | Fever, diarrhea, cough | NR         |
|                                   |               | CTRL | 446             | 280/166 | 24.41±3.04  | 7.83±1.29  | -1.76±1.13    | 9                | P          | NR                     | NR         |
| Banda <i>et al.</i> , 2021 [17]   | Malawi        | ITVN | 742             | NR      | NR          | NR         | NR            | 6                | SMS+PM     | NR                     | NR         |
|                                   |               | CTRL | 250             | NR      | NR          | NR         | NR            | 6                | P          | NR                     | NR         |
| Irena <i>et al.</i> , 2015 [15]   | Zambia        | ITVN | 824             | 397/427 | 17±1.53     | 11.5±1.2   | NR            | 14               | SMS        | NR                     | low        |
|                                   |               | CTRL |                 |         | 17±1.57     | 11.0±1.5   | NR            | 14               | P          | NR                     | NR         |

+, combined; CTRL, control; FSMS, milk-free soya-maize-sorghum; ITVN, intervention; MSMS, minimal-milk-containing soya-maize-sorghum; MUAC, mid upper arm circumference; NR, Not Reported; P, peanut; PM, peanut and milk, SMS, milk-soya-maize-sorghum; W-f-L Z Score, weight-for-length Z Score.

### Quality Appraisal

The results of the risk-of-bias assessment for all included studies are presented in **Figure 2**. A total of four studies pass all of Cochrane's risk-of-bias criteria, indicating them as high-quality studies. However, study by Irena *et al.* (2015) [15] was marked with having some concerns in the randomization process, specifically related to an imbalance number of participants between the intervention and control groups concomitant to initial low acceptance of SMS-RUTF.



Figure 2. Traffic light plot (a) and summary plot (b) of the quality of the included studies based on RoB 2.0.

### Effect on recovery

Based on the pooled estimate, children receiving SMS-RUTF was 0.77 times (95% CI: 0.66–0.90) less likely to be recovered from SAM as compared to PM-RUTF (**Figure 3**). Statistical significance was obtained in the pooled estimate ( $p < 0.01$ ), with heterogeneity can be neglected ( $I^2 = 0\%$ ) (**Figure 3**).

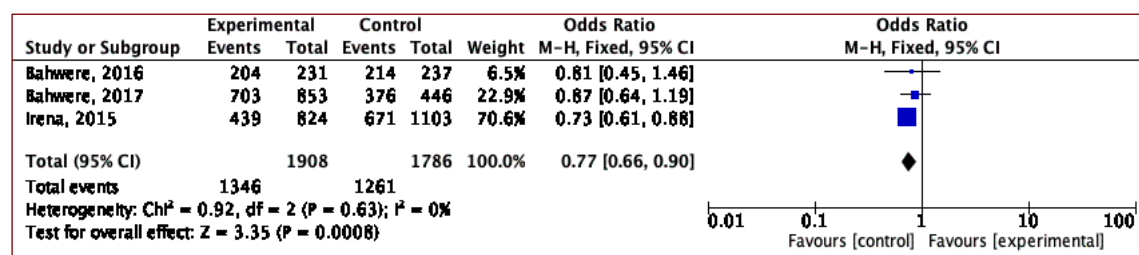


Figure 3. Forest plot for the effect of SMS-RUTF on recovery as compared to control (PM-RUTF).

### Effect on mortality

Pooled estimate for the odds of mortality between SMS-RUTF (intervention) and PM-RUTF (control) groups is presented in **Figure 4**. Odds of mortality was similar between the two groups



with PM-RUTF and SMS-RUTF ( $p=0.22$ ). The heterogeneity was not observable through  $I^2$ -statistics ( $I^2=0\%$ ).

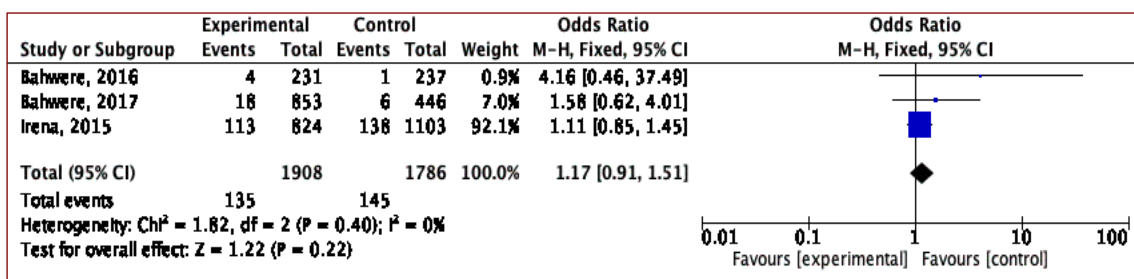


Figure 4. Forest plot for the effect of SMS-RUTF on mortality as compared to control (PM-RUTF).

### Effect on weight gain

There are two studies reporting intervention versus control outcomes related to mortality rates, and therefore included in the pooled estimate (Figure 5). Those receiving SMS-RUTF has a lower weight gain as compared to PM-RUTF with a statistical significance of  $p < 0.01$ . The mean difference was  $-1.00$  kg (95% CI:  $-1.25, -0.75$ ). No heterogeneity was observed in the pooled estimate ( $I^2=0\%$ ) (Figure 5).

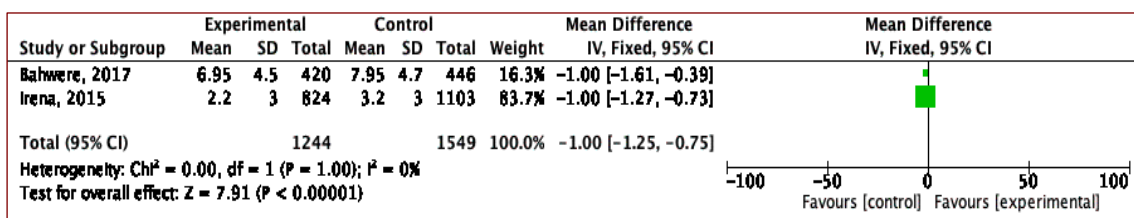
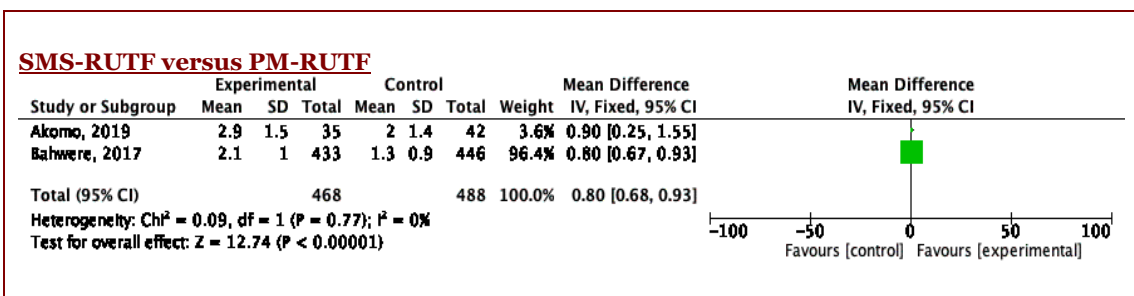


Figure 5. Forest plot for the effect of SMS-RUTF on weight gain as compared to control (PM-RUTF).

### Effect on hemoglobin level

Comparison between MSMS-RUTF and FSMS-RUTF was reported in a single study, where MSMS-RUTF was found to be better in increasing hemoglobin level than FSMS-RUTF [18]. The MD of hemoglobin level increase between groups receiving MSMS-RUTF and PM-RUTF was  $0.30$  g/dL [18]. Pooled estimates were carried out for two studies comparing MSMS-RUTF with control [4,10]. The results of the pooled estimates are presented in Figure 6, revealing a significant increase of hemoglobin level in intervention group ( $p < 0.01$ ). The total MD was  $0.80$  g/dL with 95% CI ranging from  $0.68$  g/dL to  $0.93$  g/dL. A comparison between FSMS-RUTF and PM-RUTF was also carried out in pooled estimates, where the results are also presented in Figure 6. Significantly higher hemoglobin level was observed in FSMS-RUTF group as compared to control ( $p < 0.01$ , MD:  $0.50$  (95% CI:  $0.37-0.64$ )). No heterogeneity was observed in both pooled analyses according to  $I^2$ -statistics ( $I^2=0\%$ ).



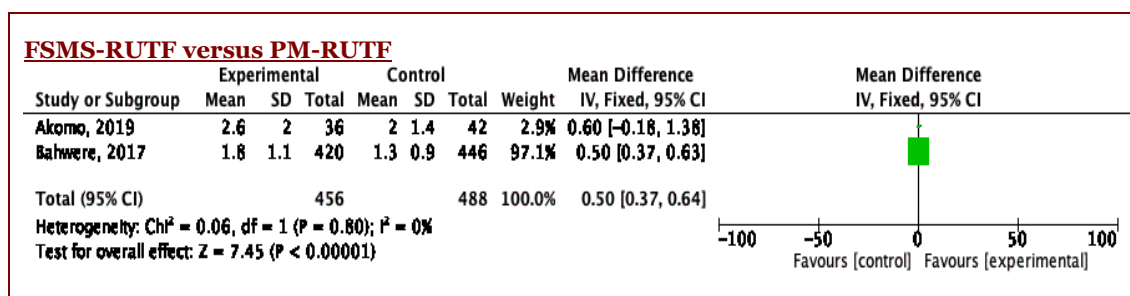


Figure 6. Forest plot for the effect of MSMS-RUTF and FSMS-RUTF in increasing hemoglobin level as compared to control (PM-RUTF).

## Discussion

The latest guidelines recommend that at least 50% of the protein in RUTF should be derived from milk products due to their superior protein quality compared to ingredients like peanuts [1]. It is crucial to acknowledge that milk is a costly component in standard RUTF, emphasizing the need to explore alternative therapeutic diets using locally available nutrient-dense foods [1]. SMS-RUTF is one of the solutions for this problem. There are two kinds of its formulation, one containing no milk (FSMS-RUTF) and the other 9% milk (MSMS-RUTF) that was designed to reach the WHO recommendations for RUTF mineral and vitamin levels [23].

Findings of this present study indicate that SMS-RUTF is inferior in ameliorating SAM among children, based on the recovery and weight gain. Similarly, a previous meta-analysis also suggested that PM-RUTF was found to be better than FSMS-RUTF or MSMS-RUTF in terms of weight gain, recovery rate, and Weight-for-Age Z-score (WAZ) [24]. Soya-based and fish-based wafer RUTF are included in the aforementioned study [24]. Our findings are corroborated by a previous study which revealed superior efficacy of PM-RUTF as compared to FSMS-RUTF or MSMS-RUTF in promoting weight gain [25]. Faster recovery was also reported in groups receiving RUTF and F100 [25]. Another systematic review also concluded that PM-RUTF is better than homemade RUTF which was prepared using locally available ingredients [15]. Administration of PM-RUTF has also been associated with lower chance of relapse [15].

SMS-RUTF higher efficacy in increasing hemoglobin levels, as compared to PM-RUTF, was found in this present study. This finding has never been revealed in previous meta-analyses. This efficacy suggests that SMS-RUTF can be used to ameliorate anemia which is an associated factor of poor nutrition. In the individual study, MSMS-RUTF was reported to outperform FSMS-RUTF in increasing hemoglobin levels [18].

Due to its high casein and calcium contents, cow's milk hinders the absorption of iron from other foods in the digestive tract, suggesting an inverse relationship between PM-RUTF and iron absorption, hence low hemoglobin [26]. Iron, zinc, and vitamin C levels in FSMS-RUTF and MSMS-RUTF were increased to attain a phytic acid/iron molar ratio, ascorbic acid/iron weight ratio, and zinc/iron weight ratio [23]. Vitamin C enhances iron absorption by interacting with non-heme iron and convert it to its more absorbable form [27].

The side effects (such as dizziness, fever, cough, and flatulence) of FSMS-RUTF or MSMS-RUTF are minimal and similar to the PM-RUTF. Notably, the key concern is the lower acceptability of FSMS-RUTF or MSMS-RUTF compared to PM-RUTF. Reports suggest that the reasons for this are related to the packaging and taste [15]. Therefore, we recommend further research to address these issues as they significantly impact both the attitude and willingness of children to consume the product. However, the attitude and willingness might be biased by the non-blinding protocol which affected the preference of the children.

The present systematic review has several limitations, one of which is the authors did not search for data in the grey literature such as government or non-governmental organizations sources. Only a few studies being included in the meta-analysis suggests the requirement of judicious interpretation of the results. In addition, this systematic review lacks a cost-effectiveness evaluation due to lack of data availability. Despite SMS-RUTF not being superior to



the standard in the rehabilitation of severe acute malnutrition, it still presents itself as a viable alternative for SAM children with anemia.

## Conclusion

Our findings suggest that FSMS-RUTF or MSMS-RUTF has lower efficacy as indicated by lower odds of recovery and lower weight gain than PM-RUTF. No statistical difference of mortality odds between the intervention (FSMS-RUTF or MSMS-RUTF) and control (PM-RUTF). The absence of heterogeneity suggests the reliability of this data, especially with large pooled sample size reaching more than five thousand. Interestingly, the PM-RUTF alternatives (FSMS-RUTF and MSMS-RUTF) showed superior efficacy in increasing hemoglobin level. Therefore, FSMS-RUTF and MSMS-RUTF can be used in managing anemia. It is also worth to consider administering FSMS-RUTF and MSMS-RUTF for children with SAM and anemia. FSMS-RUTF and MSMS-RUTF were designed as alternatives to replace or reduce milk content in RUTF because of economic reasons. Thus, it is of importance for future study to investigate the cost-effectiveness of both FSMS-RUTF and MSMS-RUTF. Moreover, improving the appearance of FSMS-RUTF and MSMS-RUTF packaging could potentially increase the acceptance. As FSMS-RUTF and MSMS-RUTF replace the protein source in RUTF, it is also interesting to include the investigation of metabolomic profile of these children.

## Ethics approval

Not applicable.

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## Competing interests

The authors declare that there is no conflict of interest.

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## Underlying data

All data underlying the results are available as part of the article and no additional source data are required. Supplementary files are available on Figshare (<https://doi.org/10.6084/m9.figshare.24922944>).

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