WHO guideline

on the dairy protein content in ready-to-use therapeutic foods for treatment of uncomplicated severe acute malnutrition

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Publication history

This is a new World Health Organization (WHO) guideline that updates the specific recommendation in the technical annex of the 2007 Joint Statement by WHO, the World Food Programme (WFP), the United Nations System Standing Committee on Nutrition (UNSSCN) and the United Nations Children's Fund (UNICEF) on community-based management of severe acute malnutrition, which states that at least 50% of protein in ready-to-use therapeutic foods (RUTF) should come from dairy products.

The rigorous procedures described in the *WHO handbook for guideline development, 2nd edition* were followed in producing this guideline. This document presents the direct and indirect evidence that served to inform the recommendation herein.

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This guideline was coordinated by the World Health Organization (WHO) Actions in Health Systems Unit, Department of Nutrition and Food Safety. Dr Jaden Bendabenda and Zita Weise Prinzo prepared this document.

WHO acknowledges the technical guidance from the members of the WHO steering committee for this normative work (in alphabetical order): Mr Filiberto Beltran, Nutrition and Food Safety; Sophie Boisson, Water, Sanitation and Hygiene; Bernadette Cappello, Essential Medicines; Adelheid Marschang, Emergencies; Dr Jason Montez, Nutrition and Food Safety; Satoko Murakami, Nutrition and Food Safety; Adama Diop Ndiaye, Gender, Equity and Human Rights; Nigel Rollins, Maternal, Newborn, Child and Adolescent Health; and Pura Solon, Maternal, Newborn, Child and Adolescent Health; as well as Regional Advisors from all six WHO regions. The steering committee also acknowledges the leadership within the Department of Nutrition and Food Safety (Dr Francesco Branca, Dr Laurence Grummer-Strawn, and Dr Juan Pablo Peña-Rosas) for their guidance during the entire process.

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Abbreviations

CI	confidence interval
EPOC	[Cochrane] Effective Practice and Organisation of Care [group]
FAO	Food and Agriculture Organization of the United Nations
GPW13	WHO's Thirteenth General Programme of Work
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRADE-CERQual	GRADE Confidence in the Evidence from Reviews of Qualitative research
LAZ	length-for-age Z-score
MUAC	mid upper-arm circumference
PICO	population, intervention, comparator and outcomes
PROSPERO	International Prospective Register of Systematic Reviews
RCT	randomized controlled trial
RoB 2	Version 2 of the Cochrane risk-of-bias tool for randomized trials
RR	risk ratio
RUTF	ready-to-use therapeutic foods
SDGs	Sustainable Development Goals
SMD	standardized mean difference
UNICEF	United Nations Children's Fund
UNSSCN	United Nations System Standing Committee on Nutrition
WAZ	weight-for-age Z-score
WHO	World Health Organization
WFP	World Food Programme
WLZ	weight-for-length Z-score

WHO guideline[1] on the dairy protein content in ready-to-use therapeutic foods for treatment of uncomplicated severe acute malnutrition

Executive summary

Purpose of the guideline

This WHO guideline is an update of the specific recommendation in the technical annex of the 2007 Joint Statement by the World Health Organization (WHO), the World Food Programme (WFP), the United Nations System Standing Committee on Nutrition (UNSSCN) and the United Nations Children's Fund (UNICEF) on community-based management of severe acute malnutrition, which states that at least 50% of the proteins in ready-to-use therapeutic foods (RUTF) should come from dairy products. When this Joint Statement was released, the only RUTF formulation available contained dairy as the primary source of protein. Recently, alternative RUTF formulations with different sources of protein have been tested in several trials. The aim of these alternative RUTF formulations is to reduce the production cost of RUTF by partially or fully replacing dairy protein with cheaper and/or locally available options. Reducing the cost of RUTF would increase access to treatment for children with severe acute malnutrition. This guideline provides global, evidence-informed recommendations focusing on whether reduced dairy or non-dairy RUTF should be used for treating uncomplicated severe acute malnutrition.

Guideline development methodology

WHO developed the present evidence-informed recommendations using the procedures outlined in the *WHO handbook for guideline development, 2nd edition*. The steps in this process include: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations, including research priorities; and planning for (v) dissemination; (vi) implementation, equity and ethical considerations; and (vii) impact evaluation and updating of the guideline. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was followed to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews.

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[1] This publication is a World Health Organization (WHO) guideline. A WHO guideline is any document containing WHO recommendations about health interventions, whether clinical, public health or policy interventions. A standard guideline is produced in response to a request for guidance in relation to a change in practice, or controversy in a single clinical or policy area, and is not expected to cover the full scope of the condition or public health problem. A recommendation provides information about what policy-makers, health care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

The initial scoping of the guideline was done by the guideline development group in a meeting held on 7 November 2019 via a virtual platform. The development and finalization of the evidence-informed recommendations were done by the guideline development group in a meeting held from 21 to 24 July 2020 via a virtual platform. Four experts served as technical peer reviewers of this guideline.

Available evidence

Three related key questions were formulated in the population, intervention, comparator and outcomes (PICO) format, when appropriate, as follows.

1. What is the effect of RUTF containing alternative sources of protein (non-dairy, or containing less than 50% of protein from dairy) compared to RUTF as specified by WHO (2007) (at least 50% of protein from dairy products) in terms of efficacy, effectiveness and safety in treating infants and children aged 6 months or older with uncomplicated severe acute malnutrition?
2. What is the effect of RUTF containing alternative sources of protein (non-dairy, or containing less than 50% of protein from dairy) compared to RUTF as specified by WHO (2007) (at least 50% of protein from dairy products) in terms of values and preferences (cultural, religious, etc.), inter/intra-household sharing, availability, acceptability, adherence, equity, (including gender-related issues), feasibility, accessibility and sustainability in treating infants and children aged 6 months or older with uncomplicated severe acute malnutrition?
3. What is the cost-effectiveness of RUTF containing alternative sources of protein (non-dairy, or containing less than 50% of protein from dairy) compared to RUTF as specified by WHO (2007) (at least 50% of protein from dairy products) in the cost of production (ingredients, quality control), cost per death averted, cost per disability-adjusted life year averted, as well as contribution of the RUTF formulation to the cost of delivery of the entire programme? Does the cost-effectiveness vary significantly in different settings with different prevalence/incidence of severe acute malnutrition, population density and coverage?

The available evidence included two systematic reviews (for questions 1 and 2) that followed the procedures in the *Cochrane handbook for systematic reviews of interventions*. There were no published trials on the cost-effectiveness of the interventions. The evidence on costs and resource implications for different RUTF formulations was taken from the UNICEF Supply Division, which compiles data of suppliers for medical commodities. The certainty of evidence for the outcomes ranged from very low to high, with all outcomes consistent in the direction favouring standard RUTF or no difference between the RUTF formulations with reduced/no dairy and standard RUTF. The guideline development group therefore determined the overall certainty across outcomes to be moderate.[1]

An evidence-to-decision framework was used to lead discussion and decision-making. This included the following considerations: (i) the certainty of the evidence across outcomes critical to decision-making; (ii) the balance of benefits and harms; (iii) values and preferences related to the recommended intervention in different settings and for different stakeholders, including the populations at risk; (iv) the acceptability of the intervention among key stakeholders; (v) resource

[1] According to GRADE, high certainty evidence indicates that we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty evidence indicates that we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty evidence indicates that our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty evidence indicates that we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

implications for programme managers; (vi) equity; and (vii) the feasibility of implementation of the intervention.

Recommendation and rationale

Recommendation

Standard RUTF (with at least 50% of protein coming from dairy products) is recommended for outpatient treatment of children with severe acute malnutrition. Use of RUTF formulations with less than 50% of protein from dairy products for outpatient treatment of children with severe acute malnutrition is encouraged within research and evaluation settings (*conditional recommendation*;[1] *moderate certainty of evidence*).

Rationale

The available evidence was not enough to justify a change in the current recommendation that RUTF should have at least 50% of protein coming from dairy. The efficacy outcomes favoured the standard RUTF, while there were no robust data from producers to demonstrate that reducing the dairy content will reduce the costs and resource requirements of RUTF. The group therefore did not recommend the use of the reduced/no dairy formulations but noted the potential of these alternative formulations if more evidence of efficacy and cost-effectiveness is generated.

Research gaps

Discussions between the members of the guideline development group highlighted the research needed to provide further evidence, as follows.

- Continuing the search for alternative RUTF formulations with no dairy or less than 50% of protein from dairy products. Well designed studies are required to demonstrate further evidence of efficacy, cost-effectiveness and acceptability of different formulations, including considerations of age, breastfeeding status, severe acute malnutrition phenotype and geographical location, among others.
- Determining the optimal level of protein in RUTF beyond the current limits (10–12% of total energy), which were based on protein content in the habitual diets consumed by well nourished children in rich countries.
- Determining the optimal content of dairy products in RUTF. The minimum of 50% of protein in RUTF coming from dairy products set in the 2007 Joint Statement was chosen for practical reasons as it corresponded to what was already in the then existing and tested RUTF, but there is no evidence that 50% is the appropriate limit. Studies are needed to demonstrate whether increasing the proportion of protein from dairy in RUTF can lead to better outcomes.
- Determining the optimal dose of RUTF that is cost-effective. One potential strategy to reduce the cost of treatment for severe acute malnutrition is by reducing the dose or quantities of RUTF required for recovery; however, the efficacy and cost savings attributed to this strategy need to be demonstrated.

[1] A conditional recommendation is one for which the guideline development group concludes that the desirable effects of adherence probably outweigh the undesirable effects, although the trade-offs are uncertain. Implications of a conditional recommendation for populations are that while some people would desire the intervention, a considerable proportion would not. With regard to policy-makers, a conditional recommendation means that there is a need for substantial debate and involvement from stakeholders before considering the adoption of the intervention in each setting.

Scope and purpose

This WHO guideline is an update of the specific recommendation in the technical annex of the 2007 Joint Statement by WHO, WFP, UNSSCN and UNICEF on community-based management of severe acute malnutrition, which states that at least 50% of the proteins in RUTF should come from dairy products (WHO, 2007). When this Joint Statement was released, the only RUTF formulation available contained dairy as the primary source of protein. Recently, alternative RUTF formulations with different sources of protein have been tested in several trials. The aim of these alternative RUTF formulations is to reduce the production cost of RUTF by partially or fully replacing dairy protein with cheaper and/or locally available options. Reducing the cost of RUTF would increase access to treatment for children with severe acute malnutrition.

Member States and United Nations partners requested WHO's rigorous evaluation of the evidence on the efficacy of these innovative and novel RUTF formulations which have potential to increase coverage in the treatment of severe acute malnutrition in children. This guideline provides global, evidence-informed recommendations focusing on whether reduced dairy or non-dairy RUTF should be used for treating uncomplicated severe acute malnutrition.

Background

The global burden of severe acute malnutrition

Globally, an estimated 14.3 million children aged 6–59 months suffered from severe acute malnutrition in 2019 (UNICEF, WHO & World Bank, 2020), defined as weight-for-length Z-score (WLZ) <–3 standard deviations and/or mid upper-arm circumference (MUAC) <115 mm, and/or presence of bilateral pitting oedema (WHO, 2009). Child undernutrition is a major global health problem, contributing to child morbidity and mortality, impaired intellectual development, suboptimal adult work capacity and increased risk of diseases in adulthood (Black et al., 2013). Malnourished children, particularly those with severe acute malnutrition, have a higher risk of death from common childhood illnesses, with 45% of deaths in children aged under 5 years attributed to malnutrition (UN IGME, 2019).

Most children aged 6 months or older with severe acute malnutrition can be safely treated in their communities without requiring admission to a health facility or a therapeutic feeding centre. This community-based approach involves timely detection of severe acute malnutrition in the community, quick assessment of appetite, and treating those without medical complications with ready-to-use therapeutic foods (RUTF), combined with basic orally-administered medication to treat infections (WHO, 2007, 2013).

History of RUTF

Community-based management of children with uncomplicated severe acute malnutrition requires safe, palatable foods with a high energy content and adequate amounts of protein, vitamins and minerals, such as RUTF.

First developed in 1996, RUTF are soft or crushable foods that can be consumed easily by children from the age of 6 months without adding water. Prior to the development of RUTF, children with severe acute malnutrition were treated with F-100, a therapeutic formulation that requires preparation and administration by qualified health workers, used only in hospitals (WHO, 1999). In contrast, RUTF can be used safely at home without refrigeration and even in areas where hygiene conditions are not optimal.

When there are no medical complications, a severely malnourished child who has appetite is given a standard dose of RUTF adjusted to their weight. Guided by appetite, the children consume the food at home, directly from the package, with supervision from their caregivers, at any time of the day or night. A child being treated for severe acute malnutrition generally requires a total of 10–15 kg of RUTF, consumed over a period of six to eight weeks (WHO, 2007).

Composition of RUTF

The most common formulation of RUTF (referred to as standard RUTF in this document) consists of four food ingredients (milk powder, peanut paste, vegetable oil and sugar) and multiple micronutrients to provide a complete complement of vitamins and minerals. The choice of food ingredients may be adjusted (usually by replacing peanuts with other legumes or cereals) depending on local availability, cost and acceptability, but the nutritional composition must comply with the 2007 Joint Statement (see Annex 1).

Protein quality and quantity in RUTF

Protein requirements during recovery from severe acute malnutrition are higher than during periods of normal growth (Pencharz, 2010). Severe acute malnutrition is also associated with chronic intestinal dysfunction with reduced nutrient absorptive capacity (Attia et al., 2016). As such, both protein quality and quantity of therapeutic foods are important for optimal recovery from severe acute malnutrition. Protein quality refers to the digestibility, bioavailability and amount of each individual essential amino acid, whereas protein quantity refers to the total amount of protein.

In 2018, an Expert Working Group convened by the Food and Agriculture Organization of the United Nations (FAO) recommended that the protein in RUTF should be of adequate quantity and quality to support an average weight gain of 10 grams per kilogram of body weight per day for optimal recovery from severe acute malnutrition (FAO, 2018).

Alternative RUTF formulations

Milk is considered the most expensive ingredient in standard RUTF. As such, it is has been suggested that replacing dairy with alternative sources of protein can significantly reduce the costs of RUTF while maintaining the nutritional composition of RUTF recommended in the 2007 Joint Statement. These alternative formulations, if produced locally and at a lower cost, may improve scalability of treatment for severe acute malnutrition.

According to UNICEF categorization (UNICEF, 2019), alternative RUTF formulations can be grouped into three categories, as follows.

1. **Renovation:** products that use a combination of alternative cereals, legumes or grains as partial or full replacement to peanuts in the standard formulation, in addition to 50% protein sourced from dairy. These formulations are compliant with the 2007 Joint Statement.
2. **Innovation:** products that use a combination of cereals, legumes, grains and different sources of animal protein (e.g. fish, egg or insect protein) with reduced amounts of dairy protein or no dairy at all. These formulations do not comply with the 2007 Joint Statement.
3. **Novel:** products that use a combination of cereals, legumes or grains, and added amino acids and/or different amounts of added vitamins and minerals. These formulations do not comply with the 2007 Joint Statement.

Recently, these alternative RUTF formulations with different sources of protein have been tested in several trials. The primary aim of these alternative RUTF formulations is to reduce the production cost of RUTF by partially or fully replacing dairy protein with cheaper and/or locally available options.

Why is it important for WHO to develop this guideline?

Member States and United Nations partners requested WHO's rigorous evaluation of the evidence on the efficacy of these innovative and novel RUTF formulations which have potential to increase coverage in the treatment of severe acute malnutrition in children.

The updated recommendation will help Member States and their implementing partners to make informed choices on different protein sources used in RUTF for the treatment of uncomplicated severe acute malnutrition. This is critical to efforts to achieve the World Health Assembly nutrition targets for 2025, which are incorporated into the Sustainable Development Goals (SDGs), to reduce and maintain wasting at <5% (WHO, 2018b), as well as SDG target 3.2 to end preventable deaths of newborns and children under 5 years of age by 2030 (United Nations, 2020).

WHO's Thirteenth General Programme of Work (GPW13) 2019–2023 (WHO, 2019a) focuses on delivering impact for people at the country level, in all countries – low, middle and high income – and is based on the SDGs. The three strategic priorities set out in the GPW13, referred to as the "triple billion" goals, are achieving universal health coverage, addressing health emergencies and promoting healthier populations. Nutrition, as a cross-cutting area in the health and development sectors, is an integral part of these goals (WHO, 2019a).

This is a new guideline that updates the specific recommendation in the technical annex of the 2007 Joint Statement by WHO, WFP, UNSSCN and UNICEF, which states that at least 50% of protein in RUTF should come from milk products (WHO, 2007). This work will contribute to achieving WHO's triple billion goals and the target for the reduction of wasting as given in the GWP13 impact framework.[1]

Aim of the guideline

This guideline provides global, evidence-informed recommendations focusing on whether reduced dairy or non-dairy RUTF should be used for treating uncomplicated severe acute malnutrition. This document presents the key recommendation and a summary of the supporting evidence.

Target audience

The recommendations in this guideline are intended for a global audience, including health professionals, clinicians, researchers, managers of nutrition and health programmes, public health policy-makers and their expert advisers, and decision-makers in organizations involved in the production, procurement, distribution and prescription of RUTF for the outpatient management of severe acute malnutrition in humanitarian and other settings.

The end-users of this guideline are:

- national and local policy-makers;
- implementers and managers of national and local nutrition programmes;
- nongovernmental and other organizations and professional societies involved in the planning and management of severe acute malnutrition;
- health professionals including clinicians, researchers, managers of nutrition and health programmes and public health policy-makers in all settings;
- producers and suppliers of RUTF.

Scope

This WHO guideline is an update of the specific recommendation in the technical annex of the 2007 Joint Statement on community-based management of severe acute malnutrition by WHO, WFP, UNSSCN and UNICEF, which states that at least half of the protein contained in RUTF should come from milk products (WHO, 2007). Recently, alternative RUTF formulations with different sources of protein have been tested in several trials. The primary aim of these alternative RUTF formulations is to reduce the production cost of RUTF by replacing dairy protein with cheaper and locally available ingredients. Reducing the cost of RUTF would increase access to treatment for children with severe acute malnutrition. Using locally available ingredients may also boost local production of RUTF.

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[1] WHO's GPW13 impact framework, targets and indicators, is available at: https://www.who.int/about/what-we-do/GPW13_WIF_Targets_and_Indicators_English.pdf.

Population of interest

The guideline will affect infants and young children aged 6 months or older with uncomplicated severe acute malnutrition globally.

Priority questions

Three related key questions were formulated in the population, intervention, comparator and outcomes (PICO) format, when appropriate, as follows.

1. What is the effect of RUTF containing alternative sources of protein (non-dairy, or containing less than 50% of protein from dairy) compared to RUTF as specified by WHO (2007) (at least 50% of protein from dairy products) in terms of efficacy, effectiveness and safety in treating infants and children aged 6 months or older with uncomplicated severe acute malnutrition?
2. What is the effect of RUTF containing alternative sources of protein (non-dairy, or containing less than 50% of protein from dairy) compared to RUTF as specified by WHO (2007) (at least 50% of protein from dairy products) in terms of values and preferences (cultural, religious, etc.), inter/intra-household sharing, availability, acceptability, adherence, equity, (including gender-related issues), feasibility, accessibility and sustainability in treating infants and children aged 6 months or older with uncomplicated severe acute malnutrition?
3. What is the cost-effectiveness of RUTF containing alternative sources of protein (non-dairy, or containing less than 50% of protein from dairy) compared to RUTF as specified by WHO (2007) (at least 50% of protein from dairy products) in the cost of production (ingredients, quality control), cost per death averted, cost per disability-adjusted life year averted, as well as contribution of the RUTF formulations to the cost of delivery of the entire programme? Does the cost-effectiveness vary significantly in different settings with different prevalence/incidence of severe acute malnutrition, population density and coverage?

Outcomes of interest

The following outcomes were considered important in evaluating the evidence for making the recommendations.

Effectiveness review:

- weight gain (or rate of weight gain);
- recovery (proportion recovered, time to recovery, sustained recovery);
- other outpatient therapeutic programme outcomes (default rate, relapse rate, non-response rate);
- mortality;
- anthropometry (mid-upper arm circumference [MUAC], weight-for-age Z-score [WAZ], weight-for-length Z-score [WLZ], and length-for-age Z-score [LAZ]);
- changes in body composition;
- biochemical changes.

Qualitative review:

- values and preferences;
- inter/intra-household sharing;
- availability;
- acceptability;
- equity;
- feasibility;
- accessibility;
- sustainability.

Resource use review:

- costs and resource needs.

Assessment of certainty of evidence

For the effectiveness review, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence across outcomes (Balshem et al., 2011; Guyatt et al., 2011). The outcomes were assessed for within-trial risk of bias, directness of evidence, heterogeneity, precision of estimate effects and risk of publication bias. Each outcome was given a quality rating of high, moderate, low or very low, based on these criteria.

For the qualitative review, the GRADE Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approach was used to determine the overall certainty in the evidence considering methodological limitations, relevance, coherence and adequacy of the data (Lewin et al., 2018).

Guideline development process

This guideline was developed in accordance with WHO's evidence-informed guideline development procedures, as outlined in the *WHO handbook for guideline development, 2nd edition* (WHO, 2014).

Modern processes for guideline development require a rigorous, systematic assessment of the literature, incorporating an assessment of the certainty of evidence (WHO, 2014). Thus, generating the evidence supporting this guideline required a systematic search for trials and a meta-analysis of the available data to inform the recommendations.

WHO steering committee

A WHO steering committee, led by the Department of Nutrition and Food Safety, was established in 2019 with representatives from the departments of Maternal, Newborn, Child and Adolescent Health; Emergencies; Essential Medicines; Gender, Equity and Human Rights; Water, Sanitation and Hygiene; and Regional Advisors from all six WHO regions (Annex 9). The steering committee guided the overall guideline development process, including: drafting the scope of the guideline and key questions in PICO format; identifying the systematic review teams and guideline methodologist; developing the planning proposal; selecting the guideline development group, observers and peer reviewers; overseeing the evidence retrieval, assessment and synthesis; collecting and assessing disclosures of interest; managing conflicts in consultation with the WHO Office of Compliance, Risk Management and Ethics; and convening a guideline development group meeting. After the recommendations were formulated by the guideline development group, the steering committee drafted the final guideline, including management of the peer review process. The steering committee will oversee the dissemination of the guideline.

Guideline development group

The guideline development group comprised 11 content experts with a range of technical skills in child health, nutrition, research and programmes, and with diverse perspectives, wide geographic representation and gender balance. The list of members of the guideline development group came from suggestions from WHO departments with an interest in the provision of scientific nutrition advice, WHO expert advisory panels, and previous guideline development group memberships.

The guideline development group advised WHO on: (i) the scope of the guidelines and priority questions for which systematic reviews of evidence would be commissioned; (ii) the choice of important outcomes for decision-making and developing recommendations; (iii) the interpretation of evidence with explicit consideration of the overall balance of risks and benefits; and (iv) formulating the final recommendations, taking into account existing evidence as well as diverse values and preferences.

The first meeting of the guideline development group was held in November 2019 (virtually), where the group discussed the general scope, key questions and outcomes, and the systematic reviews required to answer the key questions. In preparation for this meeting, a scoping review was conducted by the steering committee and the report was shared with the guideline development group members.

The second meeting of the guideline development group was held on 21–24 July 2020 (virtually), where the group examined the evidence available to inform the recommendation and appraised its certainty using the GRADE evidence profiles (Guyatt et al., 2013; Grade Working Group, 2018). The group interpreted the evidence, taking into consideration the intervention benefits and harms, values, resources, equity, acceptability and feasibility criteria, to guide in formulating the recommendations (Guyatt et al., 2008; Brunetti et al., 2013; Andrews J et al., 2013; Andrews JC et al., 2013; WHO, 2014; Grade Working Group, 2018). The list of the guideline development group members and their areas of expertise appears in Annex 5.

Representatives of other United Nations entities and international organizations in the field of nutrition and child health also attended the two meetings as observers. The observers participated in technical presentations and in discussions related to those presentations, providing additional information, feedback and clarification when required. They did not participate in the decision-making process of formulating the recommendations. The list of observers and organizations they represent are shown in Annex 6.

Systematic review teams

The systematic review teams provided comprehensive, objective syntheses of the evidence for two of the key questions that informed the recommendation. The findings from the systematic reviews were shared with all guideline development group members in advance of the July 2020 meeting and also presented during the meeting. The reports of the systematic reviews have been submitted for publication in peer reviewed journals. The list of systematic reviews and authors is presented in Annex 7.

Management of conflicts of interests

The steering group, in compliance with the WHO guidelines for declaration of interests for WHO experts[1] and in collaboration with the WHO Office of Compliance, Risk Management and Ethics, managed the potential conflicts of interests. All potential guideline development group members were asked to fill in and sign the standard WHO declaration of interests and confidentiality undertaking forms. An updated curriculum vitae was also required from each prospective member of the guideline development group, as they participate in their individual capacity and not as institutional representatives.

The steering group reviewed the declarations of interest statements and the curriculum vitae to identify potential guideline development group members. Information from the internet or media were gathered to identify any public statements made or positions held by the prospective guideline development group members and experts on the topic of RUTF. These were assessed for intellectual bias that may be perceived to affect, or may affect, impartiality. All concerns or potential issues were discussed with the WHO Office of Compliance, Risk Management and Ethics. All potential conflicts of interest were managed on a case-by-case basis.

Upon review of the declarations of interests and consultation with the WHO legal department, one potential member was deemed to have conflicts of interest (having once received a research grant from the dairy industry) and therefore was excluded from the group. The rest of the potential members were deemed to have no perceived or real conflicts of interests on the topic. At the beginning of both meetings of the guideline development group, the members were asked to verbally declare their conflicts of interest.

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[1] Guidelines for declaration of interests (WHO experts) are available at: https://www.who.int/about/ethics/doi-guide-EN.pdf?ua=1.

The names of the guideline development group, along with a description of the objectives of the meeting, were published on the WHO website for public notice and comment (WHO, 2019b). No additional information on any interests or biases relating to the individuals being considered for membership of the guideline development group were brought to light during this public notice.

Identification of priority questions and outcomes

An initial set of questions to be addressed in the guidelines was the starting point for formulating the recommendation. The questions were drafted by technical staff in the Actions in Health Systems Unit of the Department of Nutrition and Food Safety. The questions were refined and finalized by the guideline development group in November 2019. The final key questions, along with the outcomes, are listed in PICO format in Annex 2.

The population of interest was infants and children aged 6 months or older with uncomplicated severe acute malnutrition; the intervention was any RUTF formulations containing less than 50% of protein coming from dairy (reduced/non-dairy RUTF); and the comparator was any RUTF formulations containing at least 50% of protein coming from dairy (standard RUTF).

Evidence identification and retrieval

The WHO Actions in Health Systems Unit of the Department of Nutrition and Food Safety commissioned systematic reviews for the evidence to inform the recommendations on this guideline. Two systematic review teams submitted successful proposals and the protocols were published in the International Prospective Register of Systematic Reviews (PROSPERO) (Booth et al., 2020; Daniel et al., 2020).

Quality assessment and grading of evidence

Systematic reviews based on the PICO questions were used to summarize and appraise the evidence. These reviews followed the procedures of the *Cochrane handbook for systematic reviews of interventions* (Higgins et al., 2020). Each trial included in the systematic reviews was assessed for risk of bias. This was recorded and contributed towards the assessment of the overall certainty of the evidence. During the discussion and deliberations, the guideline development group reviewed the certainty, scope and trial inclusion criteria for the systematic reviews. The relative weight given to the trials was considered when evaluating the certainty assessment for each trial. The findings were synthesized with a pooled estimate of effect. The results of the systematic reviews were presented to the guideline development group, along with an assessment of the confidence in the estimates of effect for all critical outcomes.

For the effectiveness outcomes, evidence profiles were prepared according to the GRADE approach to assess the overall certainty of the evidence (Balshem et al., 2011; WHO, 2014; Grade Working Group, 2018). The certainty of evidence for each outcome was rated as "high", "moderate", "low", or "very low", based on a set of criteria including risk of bias, inconsistency, imprecision, indirectness and publication bias.

For the qualitative outcomes, GRADE-CERQual assessments of the confidence associated with the findings were performed. The Cochrane Effective Practice and Organisation of Care (EPOC) template for qualitative evidence synthesis[1] was used to report the review methods.

[1] EPOC template for qualitative evidence synthesis is available at: https://epoc.cochrane.org/news/qualitative-evidence-synthesis-template

Formulating the recommendations

The systematic reviews and the GRADE evidence profiles for each of the critical outcomes were used for formulating the recommendations. An evidence-to-decision framework was used to lead discussion and decision-making (Guyatt et al., 2008; Brunetti et al., 2013; Andrews J et al., 2013; Andrews JC et al., 2013; WHO, 2014; Grade Working Group, 2018). This framework, which considers discussions on key background information and criteria for making decisions and conclusions, was used to help the group to move from evidence to decisions.

For developing the recommendations, the guideline development group considered: the importance of the problem of severe acute malnutrition and the low treatment coverage; the evidence of the benefits and harms of the intervention compared to standard RUTF, and the certainty of this evidence; values and preferences; costs and resource requirements; and the equity, acceptability and feasibility of implementation.

Decision-making during the guideline development group meeting

The chairperson for the guideline development group was nominated at the opening of the meeting in July 2020 and the nomination was approved by the guideline development group. An independent methodologist facilitated the meeting and discussions to formulate the recommendations.

The procedures for decision-making were established at the beginning of the meeting, including a minimal set of rules for agreement and documentation of decision-making and, in case of voting, that 60% of the members would constitute a majority. More than two thirds of the guideline development group were present and participated in formulating the recommendations. If there was no unanimous consensus (primary decision rule), more time was given for deliberations and the group reached a unanimous decision on the final recommendation. The remarks and concerns from each guideline group member were recorded and will be kept on file by WHO for up to five years.

Evidence summary

To ensure that the recommendations are correctly understood and applied in practice, guideline users are encouraged to refer to the evidence summary and remarks, including the considerations on implementation.

Summary of the evidence

The evidence that informed this recommendation is based on two systematic reviews and data sourced from UNICEF. The purpose of the systematic reviews was to summarize the evidence on benefits and harms, the certainty of this evidence, values and preferences, costs and resource requirements, and the equity, acceptability and feasibility of using RUTF formulations with reduced or no dairy, compared to standard RUTF for treatment of uncomplicated severe acute malnutrition in children aged 6 months or older. The three key questions guiding the evidence review and synthesis for the recommendation are listed in the sections below. The questions and quantitative outcomes in a PICO format are presented in Annex 2.

Question 1. What is the effect of RUTF containing alternative sources of protein (non-dairy, or containing less than 50% of protein from dairy) compared to RUTF as specified by WHO (2007) (at least 50% of protein from dairy products) in terms of efficacy, effectiveness and safety in treating infants and children aged 6 months or older with uncomplicated severe acute malnutrition?

A systematic review was commissioned and registered in PROSPERO, number CRD42020160762 (Daniel et al., 2020). The full report of the systematic review can be accessed from the Advances in Nutrition journal (Potani et al., in press).

Eight articles, published from six different trials, were identified and included in this systematic review (Oakley et al., 2010; Irena et al., 2015; Bahwere et al., 2016, 2017; Sato et al., 2018; Sigh et al., 2018; Akomo et al., 2019; Hossain et al., 2019). All were individually randomized controlled trials (RCTs) apart from one cluster trial (Irena et al., 2015) with clustering at the health centre level, including a total of 24 health centres that were divided between the two trial arms.

These trials were conducted in three WHO regions, namely: Africa (Malawi [2 trials], Zambia and Democratic Republic of the Congo [1 trial each]); South-East Asia (Bangladesh [1 trial]), and the Western Pacific (Cambodia [1 trial]).

The alternative RUTF formulations used in the six trials were:

- soya RUTF containing 10% skim milk powder (Oakley et al., 2010);
- soya, maize and sorghum RUTF without dairy, used in two trials (Irena et al., 2015; Bahwere et al., 2016);
- soya, maize and sorghum RUTF without dairy but enriched with crystalline amino acids (trial arm 1), soya, maize and sorghum RUTF containing 9% skim milk powder (trial arm 2) (Bahwere et al., 2017);
- fish-based wafer RUTF without dairy (Sigh et al., 2018);
- soya RUTF without dairy (Hossain et al., 2019).

The characteristics of the six trials are summarized in Annex 3.

A total of 4827 children aged 6–59 months were included from the six trials. The largest trial was by Oakley (1874 children) (Oakley et al., 2010) and the smallest trial was by Sigh (121 children) (Sigh et al., 2018).

Risk of bias of individual trials

Risk of bias was assessed using Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) which includes assessment of biases occurring due to the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes and selection of the reported results (Sterne et al., 2019). Additional criteria examined for cluster RCTs included baseline imbalance, loss of clusters, incorrect analysis and comparability with RCTs (Sterne et al., 2019).

As shown in Fig. 1, the overall risk of bias was low but there was high risk of bias in the randomization process due to unblinding of participants and trial personnel and switching of some participants between the trial arms in two trials (Irena et al., 2015; Sigh et al., 2018).

High attrition in two trials led to some concerns of bias due to missing data (Sigh et al., 2018; Hossain et al., 2019).

Fig. 1. Risk of bias of individual trials

	D1	D2	D3	D4	D5	Overall
Oakley 2010	+	+	+	+	+	+
Irena 2015	+	x	+	–	+	x
Bahwere 2016	+	+	+	–	+	+
Bahwere 2017	+	+	+	–	+	+
Sigh 2018	+	x	–	–	–	x
Hossain 2019	+	+	x	+	+	–

Domains
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome
D5: Bias in selection of the reported result.

Judgement
x High
– Some concerns
+ Low

The main outcomes reported in these trials were:

- weight gain (or rate of weight gain);
- recovery (and time to recovery);
- mortality;
- default rates;
- non-response;
- anthropometry outcomes (i.e. MUAC, WLZ, WAZ and LAZ);
- biochemical status;
- body composition.

Weight gain

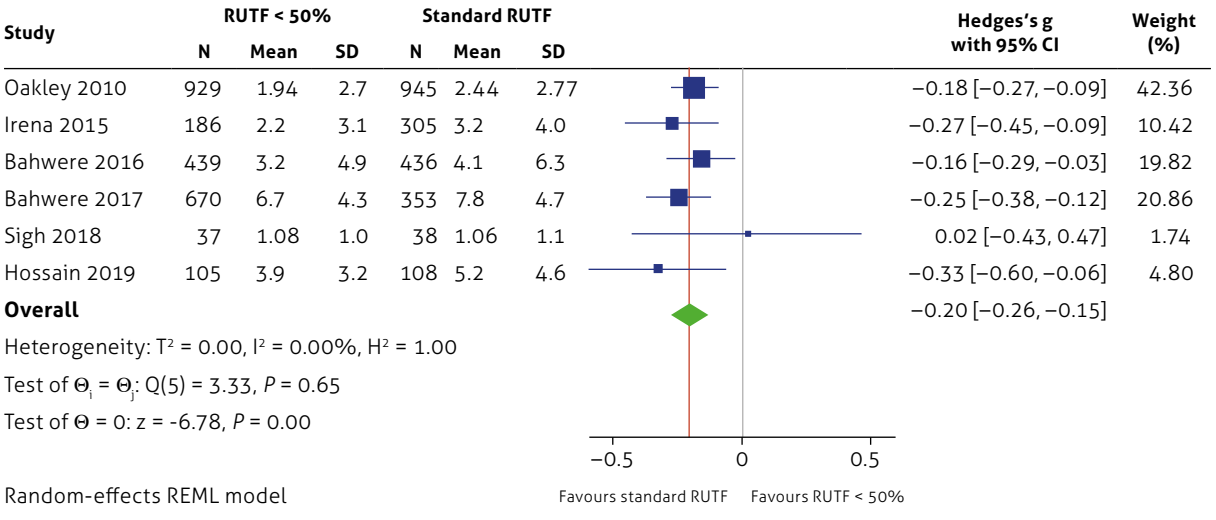
Weight gain (or rate of weight gain) was defined as gain in weight in grams per kilogram of body weight per day until recovery. The rate of weight gain was reported in all six trials. For all individual trials, apart from the Sigh 2018 trial, weight gain was significantly lower in children who consumed RUTF formulations with less than 50% of protein from dairy products compared to children who consumed standard RUTF based on Hedge's g effect sizes. The meta-analysis results showed that the overall rate of weight gain was significantly lower in children who were given RUTF formulations with less than 50% of protein from dairy products compared to standard RUTF (standardized mean difference [SMD]: –0.20, 95% confidence interval {CI} [–0.26, –0.15], $P < 0.001$, $I^2 = 0.0\%$) (Fig. 2). When excluding the Sigh 2018 trial, the only study with fish as an alternative source of protein to dairy, the meta-analysis estimates were similar (SMD: –0.2, 95% CI [–0.27, –0.15], $P < 0.001$, $I^2 = 0.0\%$).

A cumulative meta-analysis was done to assess the trends in results over time with the development of new formulations of RUTF with less than 50% of protein from dairy products. This approach demonstrates how the overall effect size changes as each individual trial is added to the meta-analysis, beginning with the earliest trial and adding trials by year (Leimu & Koricheva, 2004; Clarke, Brice & Chalmers, 2014). In this meta-analysis, the effect size remained unchanged with the addition of each subsequent trial (Fig. 3).

Subgroup meta-analysis was also done to explore differences between non-dairy and low dairy versions of RUTF. The results were not different from the primary findings (i.e. compared to standard RUTF, the weight gain mean differences were –0.23 and –0.19 for non-dairy RUTF and reduced dairy RUTF, respectively) (Fig. 4).

The certainty of the evidence for weight gain was rated high according to the GRADE approach (Table 1).

Fig. 2. Meta-analysis of the rate of weight gain in grams per kilogram of body weight per day



RUTF <50% represents RUTF with less than 50% of protein coming from dairy products.
REML: restricted maximum likelihood.

Fig. 3. Cumulative meta-analysis of the rate of weight gain in grams per kilogram of body weight per day

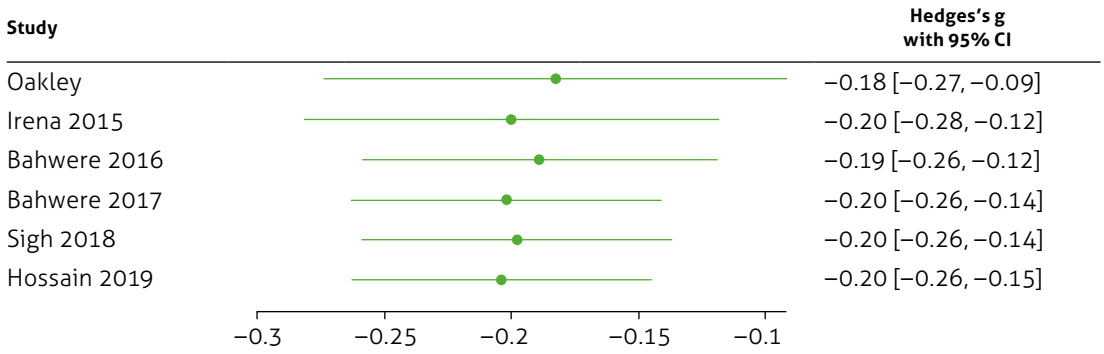
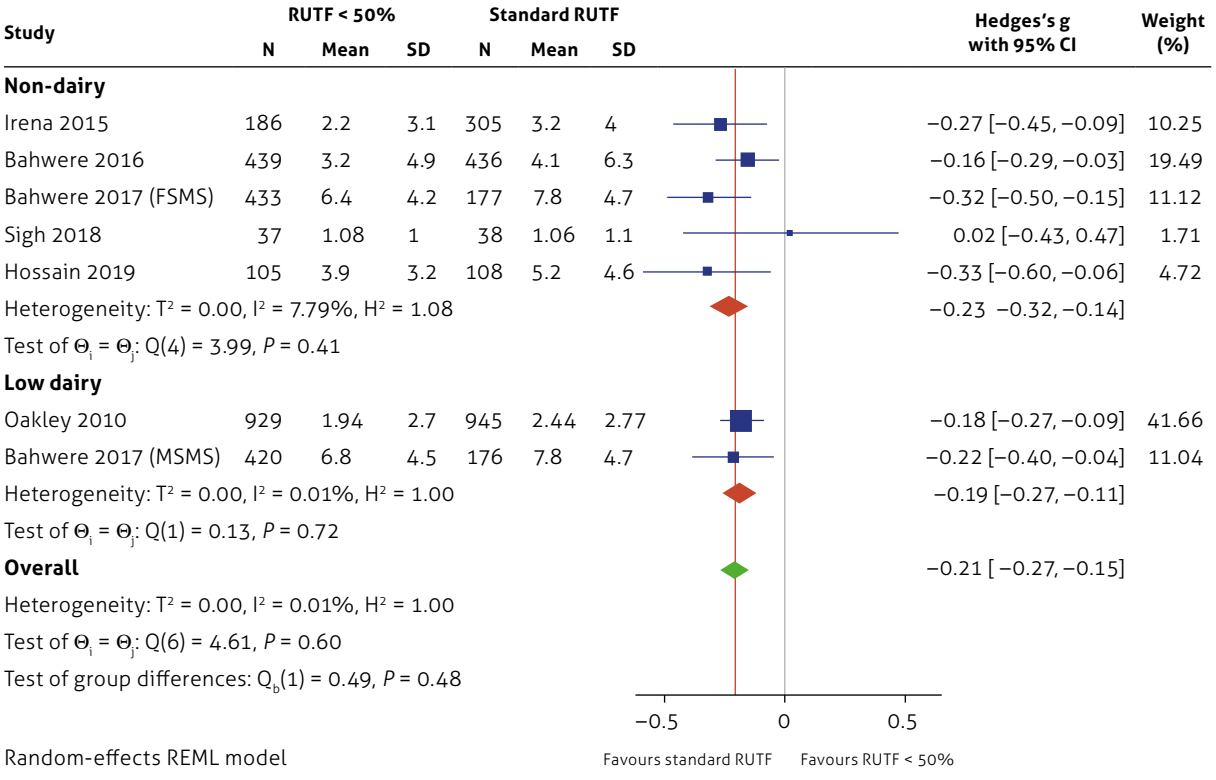


Fig. 4. Subgroup meta-analysis of the rate of weight gain in grams per kilogram of body weight per day



RUTF <50% represents RUTF with less than 50% of protein coming from dairy products.
FSMS: milk-free soya, maize and sorghum; MSMS: milk, soya, maize and sorghum; REML: restricted maximum likelihood.

Recovery

Recovery was reported in four trials (Oakley et al., 2010; Irena et al., 2015; Bahwere et al., 2016 & 2017), although defined differently in each of the trials, i.e. WLZ above –2 and no oedema (Oakley et al., 2010), and weight gain of at least 18%, MUAC above 110 mm and absence of oedema (Irena et al., 2015). The Bahwere et al. trials did not provide definitions of recovery, but in a previous trial, the authors defined recovery as weight gain of at least 15%, MUAC above 110 mm, absence of a medical complication, the absence of bilateral pitting oedema and a minimum stay in the programme of one month (Bahwere et al., 2014).

The evidence was mixed for individual trials, with two trials (Irena et al., 2015; Bahwere et al., 2016) reporting lower recovery in children consuming RUTF formulations with less than 50% of protein from dairy products than in children consuming standard RUTF. The other two trials (Oakley et al., 2010; Bahwere et al., 2017) reported similar recovery rates between the intervention and the comparator based on the risk ratios (RRs). The meta-analysis showed that providing RUTF formulations with less than 50% of protein from dairy products resulted in fewer children recovering compared to standard RUTF (RR: 0.93, 95% CI [0.87, 1.00], $P = 0.046$, $I^2 = 76.8\%$) (Fig. 5). Results from the cumulative meta-analysis across years showed similar effect sizes over time with the addition of each sequential trial (Fig. 6).

Four trials also examined the time to recovery (in days) (Irena et al., 2015; Bahwere et al., 2016 & 2017; Hossain et al., 2019). The Irena 2015 trial reported that the non-dairy RUTF was associated with a longer time to recovery compared to standard RUTF, but the other three trials did not show differences between the intervention and the comparator. The meta-analysis results indicated that the length of stay may be longer in children consuming RUTF formulations with less than 50% of protein from dairy products, although the difference was not significant (SMD: 0.20, 95% CI [–0.01, 0.41], $P = 0.06$, $I^2 = 83.3\%$) (Fig. 7).

None of the included trials examined sustained recovery because the follow-up periods were short (less than one year).

The certainty of the evidence for time to recovery was rated very low according to the GRADE approach (Table 1).

Fig. 5. Meta-analysis of recovery

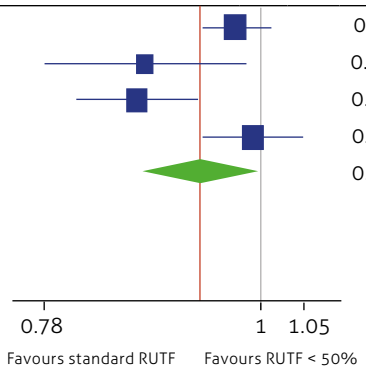
Study	RUTF < 50% Recovered		Standard RUTF Recovered		Risk ratio with 95% CI	Weight (%)
	Yes	No	Yes	No		
Oakley 2010	754	175	790	155	0.97 [0.93, 1.01]	30.48
Irena 2015	200	176	306	197	0.87 [0.78, 0.98]	17.08
Bahwere 2016	317	122	362	72	0.87 [0.81, 0.93]	25.03
Bahwere 2017	670	183	353	93	0.99 [0.94, 1.05]	27.40
Overall					0.93 [0.87, 1.00]	

Heterogeneity: $T^2 = 0.00$, $I^2 = 76.77\%$, $H^2 = 4.31$

Test of $\Theta_i = \Theta_j$: $Q(3) = 11.49$, $P = 0.01$

Test of $\Theta = 0$: $z = -2.00$, $P = 0.05$

Random-effects REML model



RUTF <50% represents RUTF with less than 50% of protein coming from dairy products.
REML: restricted maximum likelihood.

Fig. 6. Cumulative meta-analysis of recovery

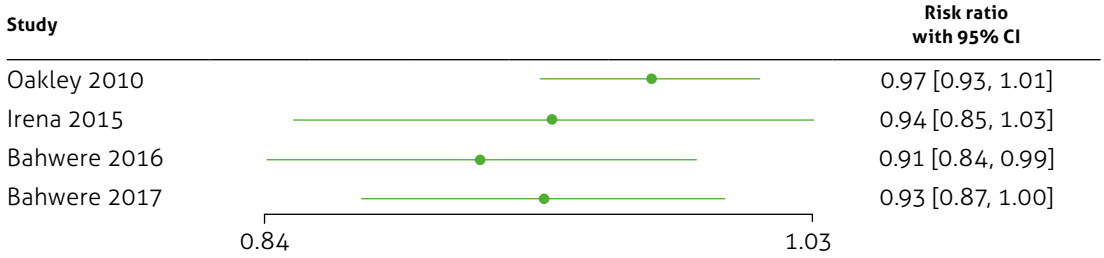
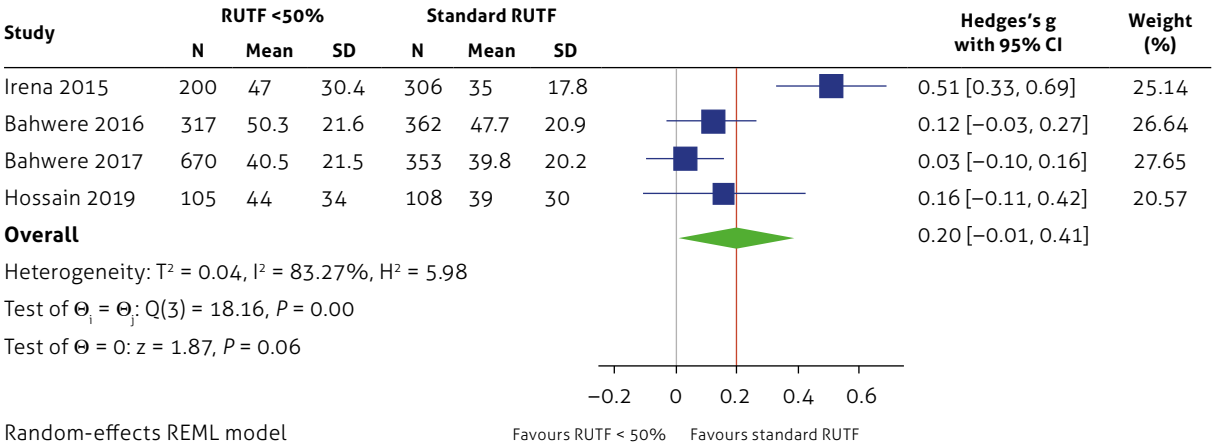


Fig. 7. Meta-analysis of time to recovery in days



RUTF <50% represents RUTF with less than 50% of protein coming from dairy products.
REML: restricted maximum likelihood.

Mortality

The percentage of children who died during the trial follow-up was reported in five trials (Oakley et al., 2010; Irena et al., 2015; Bahwere et al., 2016 & 2017; Sigh et al., 2018). One trial showed a statistically significant difference in mortality, with higher mortality in children consuming RUTF formulations with less than 50% of protein from dairy products versus standard RUTF (Bahwere et al., 2016). The other four trials did not show differences in mortality between groups. The RR of mortality appeared higher in children consuming RUTF with less than 50% of protein from dairy products, although the difference was not statistically significant (RR: 1.11, 95% CI [0.86, 1.44], $P = 0.2$, $I^2 = 0.0\%$) (Fig. 8).

The certainty of the evidence for mortality was rated low according to the GRADE approach (Table 1).

Fig. 8. Meta-analysis of mortality

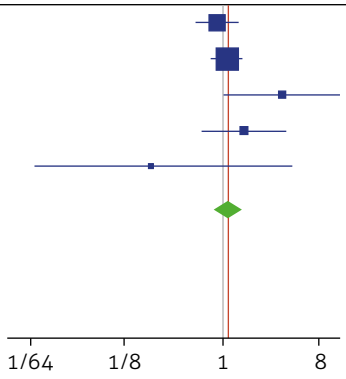
Study	RUTF < 50% Died	RUTF < 50% Survived	Standard RUTF Died	Standard RUTF Survived	Risk ratio with 95% CI	Weight (%)
Oakley 2010	30	899	34	911	0.90 [0.55, 1.45]	29.10
Irena 2015	52	325	63	441	1.10 [0.78, 1.55]	57.89
Bahwere 2016	11	428	3	431	3.62 [1.02, 12.90]	4.20
Bahwere 2017	18	835	6	440	1.57 [0.63, 3.92]	8.06
Sigh 2018	0	37	2	38	0.22 [0.01, 4.35]	0.75
Overall					1.11 [0.86, 1.44]	

Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$

Test of $\Theta_i = \Theta_j$: Q(4) = 5.77, $P = 0.22$

Test of $\Theta = 0$: z = 0.79, $P = 0.43$

Random-effects REML model



RUTF <50% represents RUTF with less than 50% of protein coming from dairy products.
REML: restricted maximum likelihood.

Other outpatient therapeutic programme outcomes

Default rates

Three trials reported default rates (defined as percentage of children who were absent for three consecutive visits if outpatient therapeutic programme was open weekly, or absent for two consecutive visits if outpatient therapeutic programme was open every two weeks) (Irena et al., 2015; Bahwere et al., 2016 & 2017).

There were no significant differences between groups in the proportion of children who defaulted in individual trials. The meta-analysis showed the RR of default to be higher in children consuming RUTF with less than 50% of protein from dairy products, although the difference was not statistically significant (RR: 1.16, 95% CI [0.99, 1.35], $P = 0.06$, $I^2 = 0.0\%$) (Fig. 9).

The certainty of the evidence for default rates was rated low according to the GRADE approach (Table 1).

Fig. 9. Meta-analysis of default rates

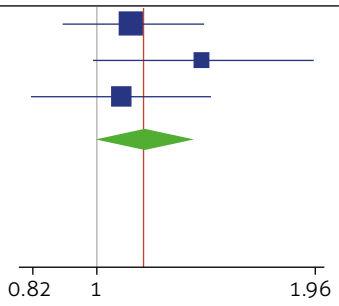
Study	RUTF < 50% Defaulted Yes	RUTF < 50% Defaulted No	Standard RUTF Defaulted Yes	Standard RUTF Defaulted No	Risk ratio with 95% CI	Weight (%)
Irena 2015	106	270	127	377	1.12 [0.90, 1.39]	48.60
Bahwere 2016	69	370	49	385	1.39 [0.99, 1.96]	20.30
Bahwere 2017	132	721	64	382	1.08 [0.82, 1.42]	31.10
Overall					1.16 [0.99, 1.35]	

Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$

Test of $\Theta_i = \Theta_j$: Q(2) = 1.47, $P = 0.48$

Test of $\Theta = 0$: z = 1.85, $P = 0.06$

Random-effects REML model



RUTF <50% represents RUTF with less than 50% of protein coming from dairy products.
REML: restricted maximum likelihood.

Non-response rates

Four trials reported non-response rates (defined as percentage of children who have not been cured within four months of treatment) (Oakley et al., 2010; Irena et al., 2015; Bahwere et al., 2016 & 2017). The Bahwere 2016 trial showed significantly higher non-response in children consuming RUTF formulations with less than 50% of protein from dairy products compared to standard RUTF according to RRs, but the other three trials did not show significant differences. The meta-analysis showed similar non-response rates in children consuming RUTF formulations with less than 50% of protein from dairy products than in children consuming standard RUTF (RR: 1.36, 95% CI [0.95, 1.94], $P = 0.09$, $I^2 = 35.8\%$) (Fig. 10).

The certainty of the evidence for non-response rates was rated moderate according to the GRADE approach (Table 1).

Fig. 10. Meta-analysis of non-response

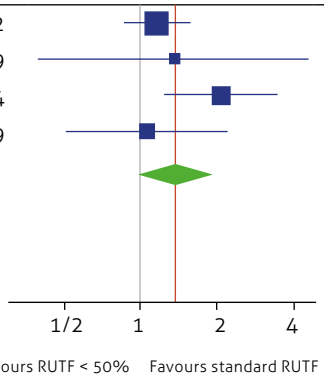
Study	RUTF < 50% Non-response		Standard RUTF Non-response		Risk ratio with 95% CI	Weight (%)
	Yes	No	Yes	No		
Oakley 2010	83	846	73	872	1.16 [0.86, 1.56]	46.74
Irena 2015	5	372	5	499	1.34 [0.39, 4.58]	7.50
Bahwere 2016	42	397	20	414	2.08 [1.24, 3.48]	28.46
Bahwere 2017	21	867	10	439	1.06 [0.50, 2.24]	17.31
Overall					1.36 [0.95, 1.94]	

Heterogeneity: $T^2 = 0.05$, $I^2 = 35.75\%$, $H^2 = 1.56$

Test of $\Theta_i = \Theta_j$: $Q(3) = 4.03$, $P = 0.26$

Test of $\Theta = 0$: $z = 1.69$, $P = 0.09$

Random-effects REML model



RUTF <50% represents RUTF with less than 50% of protein coming from dairy products.
REML: restricted maximum likelihood.

Anthropometry

At the end of follow-up, children consuming RUTF formulations with less than 50% of protein from dairy products had lower WAZ compared to children consuming standard RUTF (MD: –0.10, 95% CI [–0.20, 0.0], $P = 0.047$, $I^2 = 0.0\%$). WLZ, MUAC and LAZ at the end of follow-up were similar between the groups.

Biochemical status

Two trials, published in three articles, reported differences in anaemia and iron deficiency biomarkers between groups (Bahwere et al., 2016 & 2017; Akomo et al., 2019). The RUTF formulation without dairy and the RUTF formulation with enhanced iron content and higher phytic acid content that were used in Akomo 2019 and Bahwere 2017 trials, respectively, resulted in lower rates of anaemia and iron deficiency compared to standard RUTF (Akomo et al., 2019). Results were similar in the Bahwere 2016 trial using the version of RUTF without dairy but enhanced with iron content and higher phytic acid content, showing that this formulation improved haemoglobin concentration (difference 0.67 g/dL, 95% CI [0.42, 0.92, $P < 0.001$).

Table 1. GRADE evidence profile

Quality assessment							No. of patients		Effect		Quality
No. of trials	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RUTF < 50%	Standard RUTF	Relative (95% CI)	Absolute	
Weight gain (better indicated by higher values)											
6	RCTs and cluster RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2366	2185	–	SMD 0.20 lower (0.26 to 0.15 lower)	⨁⨁⨁⨁ HIGH
Recovery											
4	RCTs and cluster RCTs	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	1941/2597 (74.7%)	1811/2328 (77.8%)	RR 0.93 (0.87 to 1.00)	54 fewer per 1000 (from 101 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE
Time to recovery (better indicated by lower values)											
4	RCTs and cluster RCTs	Serious[2]	Serious[3]	Serious[1]	Serious[4]	None	1292	1129	–	SMD 0.20 higher (0.01 lower to 0.41 higher)	⨁◯◯◯ VERY LOW
Mortality											
5	RCTs and cluster RCTs	Serious[2]	No serious inconsistency	No serious indirectness	Serious[4]	None	111/2635 (4.2%)	108/2369 (4.6%)	RR 1.11 (0.85 to 1.44)	5 more per 1000 (from 6 fewer to 20 more)	⨁⨁◯◯ LOW
Default											
3	RCTs and cluster RCTs	Serious[2]	No serious inconsistency	No serious indirectness	Serious[4]	None	307/1668 (18.4%)	240/1384 (17.3%)	RR 1.16 (0.99 to 1.35)	28 more per 1000 (from 2 fewer to 61 more)	⨁⨁◯◯ LOW
Non-response											
4	RCTs and cluster RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	151/2633 (5.7%)	108/2332 (4.6%)	RR 1.36 (0.95 to 1.94)	17 more per 1000 (from 2 fewer to 44 more)	⨁⨁⨁◯ MODERATE
Weight-for-height Z-scores (better indicated by higher values)											
4	RCTs	Serious[2]	No serious inconsistency	No serious indirectness	Serious[4]	None	1099	1117	–	MD 0.01 higher (0.12 lower to 0.14 higher)	⨁⨁◯◯ LOW

Quality assessment							No. of patients		Effect		Quality
No. of trials	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RUTF < 50%	Standard RUTF	Relative (95% CI)	Absolute	
Mid-upper arm circumference (better indicated by higher values)											
4	RCTs	No serious risk of bias	Serious[3]	Serious[5]	No serious imprecision	None	1099	1117	–	MD 0.06 lower (0.25 lower to 0.13 higher)	⨁⨁◯◯ LOW
Weight-for-age Z-scores at end of follow-up (better indicated by higher values)											
3	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	1063	1079	–	MD 0.10 lower (0.20 lower to 0 higher)	⨁⨁⨁◯ MODERATE
Height-for-age Z-scores (better indicated by higher values)											
4	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	1099	1117	–	MD 0.02 lower (0.10 lower to 0.05 higher)	⨁⨁⨁◯ MODERATE

[1] Definition of recovery varies between trials.
[2] The amount of data from trials with a high risk of bias may affect the interpretation of results.
[3] Substantial unexplained statistical heterogeneity.
[4] Wide confidence interval around the estimate of the effect.
[5] Differences in outcome measurement (change over time and absolute values).
RUTF <50% represents RUTF with less than 50% of protein coming from dairy products.
MD: mean difference; RCT: randomized controlled trial; RR: risk ratio; SMD: standardized mean difference.

Body composition

Two trials examined the effects of the RUTF formulations with less than 50% of protein from dairy products on body composition using the deuterium dilution technique and bioimpedance analysis (Bahwere et al., 2016; Hossain et al., 2019). In the Bahwere 2016 trial, children consuming standard RUTF had a significantly higher fat-free mass index than those consuming RUTF formulations with less than 50% of protein from dairy products at the end of follow-up (difference –0.5 kg/m^2, 95% CI [–0.85, –0.15, P = 0.006) based on bioimpedance analysis. The Hossain 2019 trial showed similar results in body composition between trial groups at the end of follow-up.

Plasma amino acids were assessed in two trials across three publications, most of which did not differ between the trial groups (Oakley et al., 2010; Bahwere et al., 2016; Sigh et al., 2018). In the Bahwere 2016 trial, plasma cysteine levels were lower in children consuming RUTF formulations with less than 50% of protein from dairy products than in those consuming standard RUTF at the end of follow-up (24.96 µmol/L, 95% CI [16.70, 34.08] compared to 35.60 µmol/L, 95% CI [29.00, 39.04], P = 0.004).

Question 2: What is the effect of the RUTF containing alternative sources of protein (non-dairy, or containing less than 50% of protein from dairy) compared to RUTF as specified by WHO (2007) (at least 50% of protein from dairy products) in terms of values and preferences (cultural, religious, etc.), inter/intra-household sharing, availability, acceptability, adherence, equity, (including gender-related issues), feasibility, accessibility and sustainability in treating infants and children aged 6 months or older with uncomplicated severe acute malnutrition?

A systematic review was commissioned and registered in PROSPERO, number CRD42020167085 (Booth et al., 2020).

A total of 11 articles (from nine qualitative trials), 31 articles (from 30 acceptability trials) and seven reviews/evaluations were identified in this review.

Values and preferences: No trials reported direct comparisons of values and preferences between the RUTF formulations with less than 50% of protein from dairy products and standard RUTF. Similarly, no trials assessed differences in intrahousehold sharing, adherence or sustainability.

Acceptability: Multiple factors impact on acceptability. These include "organoleptic factors" (such as taste, smell, texture, etc.). Acceptability of food is determined by local tastes and preferences. Strong tastes and smells and unfamiliar ingredients are potential barriers to acceptability. However, these barriers can be overcome by added flavours or by encouragement from caregivers when feeding the child. Standard RUTF may perform better compared to RUTF formulations with less than 50% of protein from dairy products in terms of taste and flavour, owing to the acquired expertise from, and time spent on, product development. However, RUTF formulations with less than 50% of protein from dairy products may be more acceptable if the ingredients are locally sourced due to preference by governments and partners for locally produced foods, and a more familiar taste and ingredient for caregivers and children.

Equity: No trials reported direct comparisons of equity between the RUTF formulations with less than 50% of protein from dairy products and standard RUTF. The available evidence suggests that RUTF are frequently considered as a family resource. Therefore, sharing within the family or community and re-selling to purchase essentials may impact upon the ability of the target child to benefit. More affluent families may be able to purchase surplus RUTF. Poorer households may be unable to afford RUTF or may sell supplies perceived as surplus. However, these issues may be similar for all RUTF formulations.

Feasibility: No trials reported direct comparisons in the feasibility of producing RUTF formulations with less than 50% of protein from dairy products versus standard RUTF.

Given that the qualitative review did not find studies that made direct comparisons between the RUTF formulations with less than 50% of protein from dairy products and standard RUTF, the GRADE-CERQual tables are not presented in this guideline document.

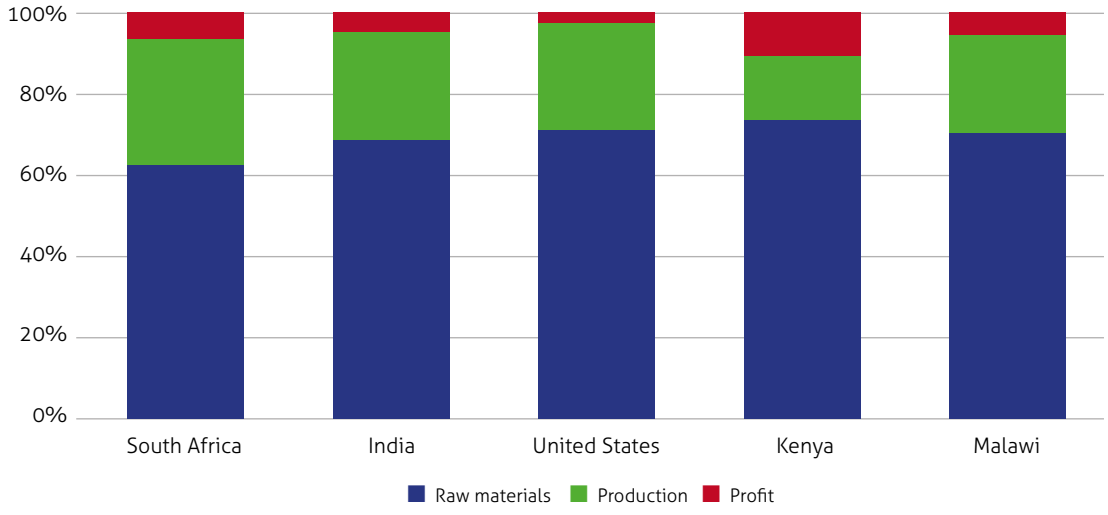
Question 3: What is the cost-effectiveness of RUTF containing alternative sources of protein (non-dairy, or containing less than 50% of protein from dairy) compared to RUTF as specified by WHO (2007) (at least 50% of protein from dairy products) in terms of cost of production (ingredients, quality control), cost per death averted, cost per disability-adjusted life year averted, as well as contribution of the RUTF formulations to the cost of delivery of the entire programme? Does the cost-effectiveness vary significantly in different settings with different prevalence/incidence of severe acute malnutrition, population density and coverage?

There were no published trials to answer this question, therefore a review was not done. The UNICEF Supply Division, which compiles data of suppliers for medical commodities, was requested to present the current data on costs and resource implications for different RUTF formulations.

According to the UNICEF data, on average, US$ 100 is required to treat a severely malnourished child (which includes: cost of RUTF, US$ 42; logistics and customs, US$ 8; and costs of running the programme, US$ 50). The cost of RUTF combines the costs of ingredients and production. RUTF ingredients account for 60–72% of the total costs, while production accounts for 17–33% of the total cost (Fig. 11).

Dairy is the most expensive ingredient in standard RUTF – on average responsible for 25% of the total cost (Table 2). The costs of the ingredients vary significantly by location and may be higher in areas where transportation costs are high and where the ingredients need to be imported.

Fig. 11. RUTF macro cost breakdown



Source: UNICEF Supply Division data.

Table 2. Standard RUTF formulation cost estimates (2013)

Ingredient	Input	Grams per sachet[a]	Average proportion of cost
Production			26%
Milk powder	17–30%	18.5g–27.5g	25%
Peanuts	25–35%	23–32 g	15%
Palm oil	2%	2g	8%
Sugar	20–28%	18.5g–26 g	6%
Packaging materials			6%
Vitamins and minerals	2.5%	2.3 g	6%
Soy or canola oil	15–20%	14g–18.5g	4%
Emulsifier (mono/diglycerides)	1–1.3%	0.9–1.2 g	2%

[a] One sachet of RUTF weighs 92 grams.
Source: UNICEF Supply Division data.

Table 3 below shows the price estimates per carton that UNICEF received from potential suppliers of either renovation RUTF formulations or innovative/novel RUTF formulations.

There has been a steady reduction in the price of standard RUTF from US$ 57 per carton[1] in 2008 to US$ 42 in 2019. This 30% price reduction has been achieved by improving efficiencies. Offshore producers have more capacity to improve efficiency and reduce RUTF price than local producers, resulting in RUTF sold by offshore producers being US$ 5 cheaper than that sold by local producers.

While the innovative/novel RUTF formulations without dairy produced locally show the largest reduction in price (5.8% median reduction), the overall price of locally produced RUTF is still higher than the offshore price. This is because local producers face more challenges in improving efficiencies necessary for price reduction.

The price estimates that UNICEF received from potential suppliers of either renovation RUTF formulations or innovative/novel RUTF formulations in 2019 showed that, in general, all suppliers were willing to lower the current price of RUTF (both dairy and non-dairy). However, the quoted prices were not much different between dairy (renovation RUTF formulations) and non-dairy RUTF (i.e. compared to standard RUTF, there was an estimated 4.8% median price reduction for renovation RUTF formulations with dairy and 4.0% median price reduction for innovative/novel RUTF formulations without dairy, when both are produced offshore).

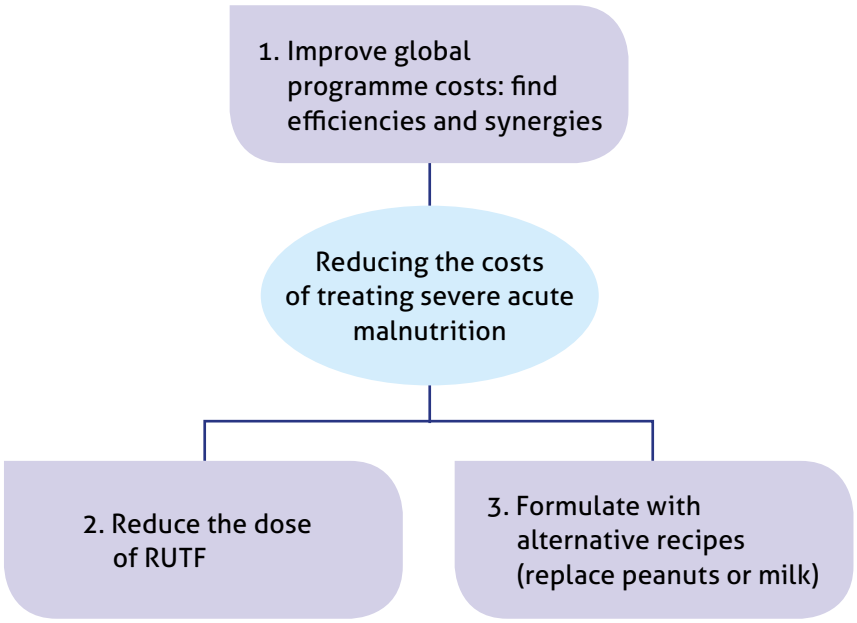
Table 3. UNICEF tender results for alternative versions of RUTF (2019)

Renovation (with dairy) (seeds, cereals or legumes replace peanuts)				Innovative/novel (without dairy) (no milk, added amino acids and different amounts of zinc, iron and vitamin C)			
Offshore		Local		Offshore		Local	
Median price reduction per carton	% median price reduction	Median price reduction per carton	% median price reduction	Median price reduction per carton	% median price reduction	Median price reduction per carton	% median price reduction
US$ 2.06	4.8%	US$ 1.93	4.0%	US$ 1.65	4.0%	US$ 2.78	5.8%

[1] One carton typically contains 150 sachets of RUTF.

These data suggest that reducing or removing dairy may result in modest reduction in the cost of treatment for children with severe acute malnutrition. There is a need to explore other strategies, such as improving inefficiencies in programming and reducing the amount of RUTF used in the treatment of severe acute malnutrition, which may help to reduce the treatment costs (Fig. 12). For example, reducing the duration of providing RUTF by one week may result in up to US$ 5.20 savings on the costs of RUTF per child. (Currently a child is given RUTF for a maximum of eight weeks.)

Fig. 12. Strategies to reduce the cost of treatment for severe acute malnutrition



Source: UNICEF Supply Division.

Summary of considerations

In determining the strength and direction of the recommendation, the guideline development group was informed by the evidence presented. When formulating the recommendation, the group also gave explicit consideration to the factors listed below. (A detailed evidence-to-decision table is presented in Annex 4.)

Balance of benefits and harms

Based on the meta-analysis of six RCTs, the RUTF formulations with less than 50% of protein from dairy products did not perform as well as standard RUTF when compared on the following outcomes: weight gain; recovery rate; and WAZ. However, mortality, default rates, non-response rates, WLZ and LAZ were similar between the RUTF formulations with less than 50% of protein from dairy products and standard RUTF. This suggests that the RUTF formulations with less than 50% of protein from dairy products are inferior to standard RUTF for some outcomes, but can perform as well as standard RUTF for other outcomes.

There was no evidence of harms reported in the trials.

The guideline development group considered that the RUTF formulations with less than 50% of protein from dairy products performed more poorly for the majority of the outcomes, but were as good as standard RUTF for some outcomes, and therefore judged the benefits of these products as small or trivial.

Certainty of evidence

The certainty of evidence for the critical outcomes ranged from very low to high, with all outcomes consistent in the direction favouring standard RUTF or no difference between the RUTF formulations with reduced/no dairy and standard RUTF. For these reasons, the guideline development group determined the overall certainty across outcomes to be moderate.

Values and preferences

The guideline development group discussed issues of values and preferences and acknowledged that the trials did not report direct comparisons between the RUTF formulations with less than 50% of protein from dairy products and standard RUTF in affecting the values and preferences of consumers and other stakeholders.

The group noted that values and preferences differ based on whether the products are produced locally or offshore, for both alternative formulations and standard RUTF. The group concluded that there is possibly important uncertainty or variability in values and preferences depending on the context.

Acceptability

The guideline development group observed that the alternative RUTF formulations will probably be acceptable depending on context, recipes and whether there is local or offshore production. In general, certain ingredients such as peanuts are less acceptable in populations that do not normally consume peanuts. In contrast, a fish-based RUTF may be poorly accepted because of strong aromas and taste of the fish. Efforts have been made to address potential barriers to

acceptability of different RUTF formulations, such as improving unfamiliar tastes or smells and investment in expertise and time spent on product development.

Equity and human rights

The importance of equal access to treatment was discussed, and the guideline development group concluded that availability of the RUTF formulations with less than 50% of protein from dairy products may help to improve access to treatment for vulnerable populations through increased volume of production, which might drive down the overall costs of RUTF. The guideline development group judged that, with more alternative RUTF formulations available on the market, equity will improve, although the current evidence is uncertain.

In all food-based interventions, intrahousehold sharing is likely to happen if the family with the severely malnourished child is also food insecure. Extremely poor households may even be forced to sell RUTF to obtain cash for purchasing basic household commodities and cheaper food that can then be shared by the whole family. In such households, RUTF may end up not being accessible to the target child. This concern applies to all RUTF formulations.

Feasibility

The guideline development group concluded that production of the RUTF formulations with less than 50% of protein from dairy products was feasible as it mostly will rely on locally available ingredients, which may be cheaper to source and more acceptable to the community. However, for plant-based RUTF formulations, local ingredients may be affected by seasonal shocks and droughts. The group noted that one trial added crystallized amino acids to improve the amino acid profile of the novel RUTF formulation. The availability and accessibility of the synthetic amino acids in low-income settings is uncertain.

Resource and cost implications

There were no published data on resource and cost implications of the RUTF formulations with less than 50% of protein from dairy products compared to standard RUTF. The guideline development group considered the programme data from UNICEF to make decisions about costs and resources.

Remarks

The remarks in this guideline are intended to demonstrate additional points that were discussed by the guideline development group before making the recommendation.

- The group discussed the significant limitation of pooling the alternative RUTF formulations in the meta-analysis. The group acknowledged the heterogeneity of the recipes used in the different trials (i.e. soya, maize, sorghum (Irena et al., 2015, Bahwere et al., 2016); soya, maize, sorghum with added synthetic amino acids (Bahwere et al., 2017); reduced dairy RUTF (Oakley et al., 2010, Bahwere et al., 2017); fish-based RUTF (Sigh et al., 2018); and soy-only RUTF (Hossain et al., 2019)). Pooling all these studies into one group may have obscured the improvements made in the development of the recipes over time. Results from sensitivity analyses were considered (e.g. a cumulative analysis done to understand the trends in results over time with the development of RUTF formulations with less than 50% of protein from dairy products) and did not significantly change the direction of effect. Any food intervention entails a combination of ingredients and nutrients whose individual effects are difficult to isolate through meta-analysis.

- Some subgroup analyses (e.g. comparing between oedematous and non-oedematous children) would have been useful to determine if the innovative or novel formulations perform differently in children with different severe acute malnutrition phenotypes. Such subgroup analyses were not possible in the meta-analysis due to small sample sizes.
- The review also showed that the RUTF formulations with less than 50% of protein from dairy products are better than standard RUTF in reducing anaemia, partly attributed to the inhibitory effect of milk protein on iron absorption (Akomo et al., 2019). The higher amounts of iron and vitamin C in RUTF formulations with less than 50% of protein from dairy products may also have been responsible for this difference. However, plant sources of protein used in the alternative RUTF formulations may also contain elements that inhibit iron absorption. This suggests that standard RUTF may be insufficient to resolve anaemia and iron deficiency in severely malnourished children. There is a need to explore RUTF formulations with varying levels of iron content as well as other means of iron supplementation.
- While removing dairy from RUTF may reduce the ingredient costs of RUTF, the decrease may not be as large as expected (about 4–5%, according to the data provided by UNICEF). If these formulations result in lower weight gain, the cost savings may be wiped out as a result of longer duration of treatment, lower recovery rates, and possibly higher rates of relapse and overall diminished nutritional status. Other strategies such as reducing the dose or quantity of RUTF given per child, reducing the costs of running the therapeutic programmes and reducing losses within the supply chain, need to be explored.
- The dilemma of balancing between suboptimal biological outcomes and possible increases in equity and acceptability that may come with introduction of the alternative formulations was acknowledged by the guideline development group. However, it was considered by the majority of the members that biological outcomes were more important.

Recommendation

Standard RUTF (with at least 50% of protein coming from dairy products) is recommended for outpatient treatment of children with severe acute malnutrition. Use of RUTF formulations with less than 50% of protein from dairy products for outpatient treatment of children with severe acute malnutrition is encouraged within research and evaluation settings (*conditional recommendation*;[1] *moderate certainty of evidence*).

Rationale

The available evidence was not enough to justify a change in the current recommendation that RUTF should have at least 50% of protein coming from dairy. The efficacy outcomes favoured the standard RUTF while there were no robust data from producers to demonstrate that reducing the dairy content will reduce the costs and resource requirements of RUTF. The group therefore did not recommend the use of the reduced/no dairy formulations, but noted the potential of these alternative formulations if more evidence of efficacy and cost-effectiveness is generated.

[1] A conditional recommendation is one for which the guideline development group concludes that the desirable effects of adherence probably outweigh the undesirable effects, although the trade-offs are uncertain. Implications of a conditional recommendation for populations are that while some people would desire the intervention, a considerable proportion would not. With regard to policy-makers, a conditional recommendation means that there is a need for substantial debate and involvement from stakeholders before considering the adoption of the intervention in each setting.

Research gaps

Discussions during the guideline development group meeting highlighted the key research gaps that need to be addressed, as follows.

1. Continuing the search for alternative RUTF formulations

The systematic review showed that RUTF formulations with no dairy or less than 50% of protein from dairy products can be as effective as standard RUTF for some outcomes including mortality, default rates, WLZ and LAZ, suggesting there is potential for these formulations; however, more (particularly multicentre) studies are needed. Further studies should aim to better understand why the RUTF formulations with no dairy or less than 50% of protein from dairy products resulted in lower weight gain than standard RUTF, despite the addition of synthetic amino acids in one of the studies. Further studies should focus on the following important areas:

- the cost-effectiveness analysis of the different formulations, which should be conducted after demonstrating the efficacy of the particular formulation;
- acceptability, cultural appropriateness (taste differences), and adherence of the populations to the different formulations;
- the role of antinutrients in plant-based RUTF formulations;
- how the different formulations affect the microbiota;
- any differences in outcomes when stratifying children by: (i) age (dairy may be more important in children aged under 2 years than in older age groups; (ii) breastfeeding status; (iii) severe acute malnutrition phenotype (i.e wasting versus oedema); and (iv) geographical location (with differences in diets).

2. Determining the optimal level of protein in RUTF

The recommended protein content of standard RUTF is 10–12% of total energy. These limits were based on very limited evidence, and are lower than the protein content in the habitual diets consumed by well nourished children in rich countries. They were derived from the 1995 F-100 specifications, based on expert advice. It would be important to determine if higher protein content (without exceeding the upper limits of safety for undernourshed children) is more effective for promotion of growth (especially in children aged under 2 years).

3. Determining the optimal content of dairy products in RUTF

The minimum of 50% of protein in RUTF coming from dairy products set in the 2007 Joint Statement was chosen for practical reasons, as it corresponded to what was already in the then existing and tested RUTF. Although the systematic review demonstrated that RUTF formulations with no dairy or less than 50% of protein from dairy products did not achieve similar weight gain as standard RUTF, there is no evidence that 50% is the appropriate limit. Studies are needed to demonstrate whether increasing the proportion of protein from dairy in RUTF can lead to better outcomes.

4. Determining the optimal dose of RUTF that is cost-effective

One potential strategy to reduce the cost of treatment for severe acute malnutrition is by reducing the dose or quantities of RUTF required for recovery; however, the efficacy and cost savings attributed to this strategy need to be demonstrated. More information needs to be collected on how the reducing of the dose will impact recovery and remedial efforts to reduce intrahousehold sharing (which diverts the treatment from the target child).

External peer review

The peer reviewers for this guideline are four experts, identified by the steering group, who provided valuable insights to the guideline document before finalizing. The peer review process focused on the following areas: (i) the clarity of the language and the presentation of the guideline; (ii) the clarity of the recommendations; and (iii) highlighting any important evidence that had not been included in the guideline.

The peer reviewers' expertise includes child health, severe acute malnutrition and research (Annex 8).

Implementation of the guideline

Implementation considerations

Member States and programmes that provide services for outpatient treatment of severe acute malnutrition in children aged 6 months or older will require this guideline when making decisions in procuring and prescribing RUTF.

The Codex Alimentarius guideline[1] (under development) will need to be aligned to the recommendation in this guideline.

The 2007 Joint Statement will need to be updated to reflect the recommendation. Researchers designing various studies on RUTF will also need to refer to this guideline document.

Engaging with multiple stakeholders and partners will be critical for making improvements and collecting evidence on innovative and novel RUTF formulations that will inform further guideline updates. Meanwhile, efforts need to be made to ensure that all children with severe acute malnutrition have access to treatment. This involves not only focusing on RUTF production, but also strengthening the entire supply chain for the products and reducing wastage, as well as reducing the overall costs of running the outpatient treatment services of severe acute malnutrition programmes. Working in collaboration with other sectors involved in child health and water, sanitation and hygiene, nutrition-sensitive interventions focusing on livelihood support will ensure a comprehensive, cross-sectoral and more sustainable approach to increasing access to treatment for vulnerable populations.

Regulatory considerations

This recommendation should be framed under the existing national strategies on management of child undernutrition. The decision to further evaluate RUTF formulations with less than 50% of protein from dairy products in research settings should be considered in the context of the national strategy, including consideration of the costs, feasibility, accessibility and acceptability of the ingredients in the RUTF product among the different stakeholders (e.g. the children, caregivers, decision-makers, law-makers, programme managers, manufacturers, industry organizations, importers, exporters, retailers and consumer organizations).

Monitoring and evaluation of guideline implementation

A plan for monitoring and evaluation with appropriate indicators, including equity-oriented indicators, is encouraged at all stages. The impact of this guideline can be evaluated within countries (i.e. monitoring and evaluation of the programmes implemented at national or regional scale) and across countries (i.e. adoption and adaptation of the guideline globally). Central to this will be availability of robust evaluation data on the use of the innovative or novel RUTF formulations to enable further guideline updates as soon as the data become available.

An efficient system for the routine collection of relevant data, including access to treatment and measures of programme performance, is critical to ensure programmes are effective and sustained drivers for the achievement of the global targets on wasting.

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[1] Information on Codex guideline for RUTF available at: http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-720-41%252FWD%252Fnf41_06e.pdf.

Dissemination and plans for updating

Dissemination

This guideline will be disseminated online through the WHO Nutrition mailing list (WHO, 2017), social media, the WHO Nutrition and Food Safety webpage (WHO, 2020) and the WHO e-Library of Evidence for Nutrition Actions (eLENA) (WHO, 2018a). eLENA compiles and displays WHO guidelines related to nutrition, along with complementary documents such as: systematic reviews and other evidence that informed the guidelines; biological and behavioural rationales; and additional resources produced by Member States and global partners. In addition, the guideline will be disseminated through a broad network of international partners including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations entities and nongovernmental organizations.

Plans for updating the guideline

This is designed to be a living guideline; as such, the WHO Secretariat will continue to monitor the progress of the proposed research agenda to improve the efficacy and acceptability of alternative formulations and robust data on cost savings. When new evidence becomes available, the Department of Nutrition and Food Safety will coordinate the guideline update, following the formal procedures of the *WHO handbook for guideline development, 2nd edition* (WHO, 2014).

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Annex 1.

Nutritional composition of RUTF

Moisture content	2.5% maximum
Energy	520–550 Kcal/100 g
Proteins	10%–12% total energy
Lipids	45%–60% total energy
Sodium	290 mg/100 g maximum
Potassium	1,110–1,400 mg/100 g
Calcium	300–600 mg/100 g
Phosphorus (excluding phytate)	300–600 mg/100 g
Magnesium	80–140 mg/100 g
Iron	10–14 mg/100 g
Zinc	11–14 mg/100 g
Copper	1.4–1.8 mg/100 g
Selenium	20–40 µg
Iodine	70–140 µg/100 g
Vitamin A	0.8–1.1 mg/100 g
Vitamin D	15–20 µg/100 g
Vitamin E	20 mg/100 g minimum
Vitamin K	15–30 µg/100 g
Vitamin B1	0.5 mg/100 g minimum
Vitamin B2	1.6 mg/100 g minimum
Vitamin C	50 mg/100 g minimum
Vitamin B6	0.6 mg/100 g minimum
Vitamin B12	1.6 µg/100 g minimum
Folic acid	200 µg/100 g minimum
Niacin	5 mg/100 g minimum
Pantothenic acid	3 mg/100 g minimum
Biotin	60 µg/100 g minimum
n-6 fatty acids	3%–10% of total energy
n-3 fatty acids	0.3%–2.5% of total energy

Annex 2.

Key questions in a population, intervention, comparator and outcomes (PICO) format

1. What is the effect of RUTF containing alternative sources of protein (non-dairy, or less than 50% of protein coming from dairy products) compared to RUTF as specified by WHO (2007) (at least 50% of protein from dairy products) in terms of efficacy, effectiveness and safety in treating infants and children aged 6 months or older with uncomplicated severe acute malnutrition?
2. What is the effect of RUTF containing alternative sources of protein (non-dairy, or less than 50% of protein coming from dairy products) compared to RUTF as specified by WHO (2007) (at least 50% of protein from dairy products) in terms of values and preferences (cultural, religious, etc.), inter/intra-household sharing, availability, acceptability, adherence, equity, (including gender-related issues), feasibility, accessibility and sustainability in treating infants and children aged 6 months or older with uncomplicated severe acute malnutrition?
3. What is the cost-effectiveness of RUTF containing alternative sources of protein (non-dairy, or less than 50% of protein coming from dairy products) compared to RUTF as specified by WHO (2007) (at least 50% of protein from dairy products) in terms of cost of production (ingredients, quality control), cost per death averted, cost per disability-adjusted life year averted, as well as contribution of the RUTF formulations to the cost of delivery of the entire programme? Does the cost-effectiveness vary significantly in different settings with different prevalence/incidence of severe acute malnutrition, population density and coverage?

The table below outlines the PICO for the quantitative outcomes (question 1).

Should RUTF with less than 50% of protein coming from dairy products versus standard RUTF be used for treating uncomplicated severe acute malnutrition in children aged 6 months or older?	
POPULATION	Infants and children aged 6 months or older with severe acute malnutrition who have appetite and no medical complications
INTERVENTION	Any RUTF containing less than 50% of protein from dairy products
COMPARISON	Standard RUTF (containing at least 50% of protein from dairy products – milk or whey)
OUTCOMES	Weight gain (or rate of weight gain) Recovery (proportion recovered, time to recovery, sustained recovery) Other outpatient therapeutic programme outcomes (default rate, relapse rate, non-response rate) Mortality Anthropometry (mid-upper arm circumference, weight-for-height, weight-for-age, height/length-for-age) Change in body composition Biochemical changes
SETTINGS	Inpatient (rehabilitation phase) and outpatient care in both emergency and stable settings

Annex 3.

Characteristics of the trials included in the systematic review for effectiveness outcomes

Study	Country setting	Study design	Baseline sample size	Severe acute malnutrition types	Age range	Description of protein source[1]
Oakley 2010	Malawi (low income)	RCT	Intervention: 929 Comparison: 945	Severe wasting and oedematous malnutrition	6–59 months	Soya RUTF containing 10% skim milk powder
Irena 2015	Zambia (low income)	Cluster RCT (clustering at the level of the health centre, 24 health centres)	Intervention: 824 (effective sample size 376) Comparison: 1103 (effective sample size 504)	Severe wasting and oedematous malnutrition	6–59 months	Soya, maize and sorghum RUTF without milk/dairy powder
Bahwere 2016	Democratic Republic of the Congo (low income)	RCT	Intervention: 439 Comparison: 436	Severe wasting and oedematous malnutrition	6–59 months	Soya, maize and sorghum RUTF without dairy
Bahwere 2017/ Sato 2018/ Akomo 2019	Malawi (low income)	RCT	Intervention 1 (FSMS-RUTF): 433 Intervention 2 (MSMS-RUTF): 420 Comparison: 446	Severe wasting and oedematous malnutrition	6–59 months	Intervention 1 (FSMS-RUTF): soya, maize and sorghum RUTF enriched with crystalline amino acids without dairy Intervention 2 (MSMS-RUTF): soya, maize and sorghum RUTF containing 9% skim milk powder
Sigh 2018	Cambodia (middle income)	RCT	Intervention: 60 Comparison: 61	Severe wasting and oedematous malnutrition	6–59 months	Fish-based wafer RUTF without dairy
Hossain 2019	Bangladesh (middle income)	RCT	Intervention: 130 Comparison: 130	Severe wasting only	6–59 months	Soya RUTF without dairy

[1] Details of the ingredients for each formulation can be found in the published papers for each study cited here.
RUTF <50% represents RUTF with less than 50% of protein coming from dairy products.
FSMS: milk-free soya, maize, and sorghum; MSMS: milk, soya, maize, and sorghum; RCT: randomized controlled trial; SAM: severe acute malnutrition.

Annex 4.

Evidence-to-decision tables

QUESTION

Should RUTF with less than 50% of protein coming from dairy products versus standard RUTF be used for treating uncomplicated severe acute malnutrition in children aged 6 months or older?	
POPULATION	Infants and children aged 6 months or older with severe acute malnutrition who have appetite and no medical complications
INTERVENTION	Any RUTF containing less than 50% of protein from dairy products
COMPARISON	Standard RUTF (containing at least 50% of protein from dairy products – milk or whey)
OUTCOMES	Weight gain (or rate of weight gain) Recovery (proportion recovered, time to recovery, sustained recovery) Other outpatient therapeutic programme outcomes (default rate, relapse rate, non-response rate) Mortality Anthropometry (mid-upper arm circumference, weight-for-height, weight-for-age, height/length-for-age) Change in body composition Biochemical changes
SETTINGS	Inpatient (rehabilitation phase) and outpatient care in both emergency and stable settings

ASSESSMENT

PROBLEM **Is the problem a priority?**		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
☒ Yes ☐ Probably yes ☐ No ☐ Probably no ☐ Uncertain ☐ Varies	An estimated 14.3 million children aged 6–59 months suffered from severe acute malnutrition in 2019.[1] Children with severe acute malnutrition have an increased risk of serious illness and death, primarily from acute infectious diseases.[2] The 2007 Joint Statement recommends treating children with uncomplicated severe acute malnutrition in the community with RUTF. The Joint Statement specifies that at least 50% of protein in RUTF should come from dairy products.[3] Milk is the most expensive ingredient in standard RUTF. RUTF formulations with reduced/no dairy may be cheaper, thereby increasing access to treatment. Currently, only 25% of children with severe acute malnutrition have access to treatment.[4] It is unclear whether RUTF formulations with reduced/no dairy are similar to standard RUTF in efficacy, effectiveness, safety, acceptability, and values and preferences, and whether they provide a cheaper option.	
BENEFITS AND HARMS **How substantial are the benefits?**		
☐ Large ☐ Moderate ☐ Small ☒ Trivial ☐ Uncertain ☐ Varies	The meta-analysis included six randomized controlled trials (RCTs) and cluster RCTs. RUTF formulations with reduced/no dairy resulted in: • lower weight gain, compared to standard RUTF: six studies, n = 4551, standard mean difference (SMD) = –0.20, 95% CI (–0.26, –0.15); • lower recovery rate, compared to standard RUTF: four studies, n=4827, risk ratio (RR) = 0.93, 95% CI (0.87, 1.00); • lower weight-for-age Z-scores compared to standard RUTF: three RCTs, n = 2142, MD –0.10, 95% CI (–0.20, 0.00); • mortality, default rates, weight-for-height Z-scores and height-for-age Z-scores were similar between the RUTF formulations with reduced/no dairy and standard RUTF.	

[1] UNICEF, WHO & World Bank. Levels and trends in child malnutrition: key findings of the 2020 edition of the joint child malnutrition estimates. Geneva: World Health Organization: 2019 (https://www.who.int/publications/i/item/jme-2020-edition, accessed 10 February 2021).

[2] McDonald CM, Olofin I, Flaxman S, Fawzi WW, Spiegelman D, Caulfield LE, et al. The effect of multiple anthropometric deficits on child mortality: meta-analysis of individual data in 10 prospective studies from developing countries. Am J Clin Nutr. 2013; 97:896–901. doi:10.3945/ajcn.112.047639.

[3] Community-based management of severe acute malnutrition. A joint statement by the World Health Organization, the World Food Programme, the United Nations System Standing Committee on Nutrition and the United Nations Children's Fund. Geneva: World Health Organization; 2007 (https://apps.who.int/iris/handle/10665/44295, accessed 23 January 2021).

[4] Expert meeting on ready-to-use-therapeutic foods (RUTF). Report 1: 2nd-3rd September 2019. Copenhagen: UNICEF Supply Division; 2019 (https://www.unicef.org/supply/documents/report-expert-meeting-ready-use-therapeutic-foods-rutf, accessed 4 September 2020).

How substantial are the harms?

☐ Large
☐ Moderate
☐ Small
☐ Trivial
☒ Uncertain
☐ Varies

No evidence of harms was reported in the studies.

What is the overall certainty of this evidence?

☐ High
☒ Moderate
☐ Low
☐ Very low

Certainty across outcomes ranged from very low to high, with all outcomes consistent in the direction favouring standard RUTF or no difference between intervention and comparison.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RUTF <50%	Standard RUTF	Relative (95% CI)	Absolute		
Weight gain (better indicated by higher values)												
6	RCTs and cluster RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2366	2185	–	SMD 0.20 lower (0.26 to 0.15 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Recovery												
4	RCTs and cluster RCTs	No serious risk of bias	No serious inconsistency	Serious	No serious imprecision	None	1941/2597 (74.7%)	1811/2328 (77.8%)	RR 0.93 (0.87 to 1.00)	54 fewer per 1000 (from 101 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Time to recovery (better indicated by lower values)												
4	RCTs and cluster RCTs	Serious	Serious	Serious	Serious	None	1292	1129	–	SMD 0.20 higher (0.01 lower to 0.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality												
5	RCTs and cluster RCTs	Serious	No serious inconsistency	No serious indirectness	Serious	None	111/2635 (4.2%)	108/2369 (4.6%)	RR 1.11 (0.86 to 1.44)	5 more per 1000 (from 6 fewer to 20 more)	⨁⨁◯◯ LOW	CRITICAL

Default												
3	RCTs and cluster RCTs	Serious	No serious inconsistency	No serious indirectness	Serious	None	307/1668 (18.4%)	240/1384 (17.3%)	RR 1.16 (0.99 to 1.35)	28 more per 1000 (from 2 fewer to 61 more)	⨁⨁◯◯ LOW	CRITICAL
Non-response												
4	RCTs and cluster RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious	None	151/2633 (5.7%)	108/2332 (4.6%)	RR 1.36 (0.95 to 1.94)	17 more per 1000 (from 2 fewer to 44 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Weight-for-height Z-scores (better indicated by higher values)												
4	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious	None	1099	1117	–	MD 0.01 higher (0.12 lower to 0.14 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Mid-upper arm circumference (better indicated by higher values)												
4	RCTs	No serious risk of bias	No serious inconsistency	Serious	No serious imprecision	None	1099	1117	–	MD 0.06 lower (0.25 lower to 0.13 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Weight-for-age Z-scores (better indicated by higher values)												
3	RCTs	No serious risk of bias	No serious inconsistency	No serious indirect-ness	Serious	None	1063	1079	–	MD 0.10 lower (0.20 lower to 0 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Height-for-age Z-scores (better indicated by higher values)												
4	RCTs	No serious risk of bias	No serious inconsistency	No serious indirect-ness	Serious	None	1099	1117	–	MD 0.02 lower (0.10 lower to 0.05 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

Risk of bias: the amount of data from studies with a high risk of bias may affect the interpretation of the results.
Inconsistency: substantial unexplained statistical heterogeneity.
Indirectness: definition of recovery varies between studies as a reason for downgrading the evidence for recovery and time to recovery; differences in outcome measurement (change over time and absolute values) as a reason for downgrading the evidence for mid-upper arm circumference.
Imprecision: wide confidence intervals around the estimate of the effect.
RUTF <50% represents RUTF with less than 50% of protein coming from dairy products.

What is the balance between the benefits and harms?		
☐ Favours reduced/no dairy RUTF ☐ Probably favours reduced/no dairy RUTF ☐ Does not favour either ☒ Probably favours standard RUTF ☐ Favours standard RUTF ☐ Uncertain ☐ Varies	RUTF formulations with reduced/no dairy resulted in lower weight gain, recovery and weight-for-age Z-scores. Mortality was similar to standard RUTF. Allergies, aflatoxin levels, etc. were not reported.	
VALUES AND PREFERENCES **How do patients value RUTF formulations with reduced/no dairy?**		
☐ Important uncertainty or variability ☒ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☐ No important uncertainty or variability ☐ No known undesirable outcomes	Nine papers reported about stakeholders' values and preferences, but none of these compared the intervention with the comparator.	

RESOURCES **How large are the resource requirements?**		
☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☒ Uncertain ☐ Varies	No published studies were found on resource requirements. According to the data from UNICEF Supply Division, there has been a steady reduction in the price of standard RUTF from US$ 57 per carton in 2008 to US$ 42 in 2019. This 30% price reduction has been achieved by improving efficiencies. Offshore producers have more capacity to improve efficiency and reduce RUTF price than local producers, resulting in RUTF sold by offshore producers being US$ 5 cheaper than that sold by local producers. While the innovative or novel RUTF formulations without dairy produced locally show the largest reduction in price (5.8% median reduction), the overall price of locally produced RUTF is still higher than the offshore price. This is because local producers face more challenges in improving efficiencies necessary for price reduction. The price estimates that UNICEF received from potential suppliers of either renovation RUTF formulations or innovative/novel RUTF formulations in 2019 showed that, in general, all suppliers were willing to lower the current price of RUTF (both dairy and non-dairy). However, the quoted prices showed not much difference between dairy (renovation RUTF formulations) and non-dairy RUTF (compared to standard RUTF, there was an estimated 4.8% median price reduction for renovation RUTF formulations with dairy and 4.0% median price reduction for innovative or novel RUTF formulations without dairy, when both are produced offshore). These data suggest that reducing or removing dairy may only result in modest reduction in the cost of treatment for children with severe acute malnutrition.	While removing dairy from RUTF may reduce the ingredient costs of RUTF, the gains are minimal (about 4–5%). If these formulations result in lower weight gain, the cost savings may be wiped out as a result of longer duration of treatment. The guideline development group acknowledged the lack of supporting data directly from producers and concluded that there was not enough information to make a comparison on resource savings accrued by reducing or removing dairy from the RUTF formulations.

Does the cost-effectiveness favour use of reduced/no dairy RUTF or standard RUTF?		
☐ Favours reduced/no dairy RUTF ☐ Probably favours reduced/no dairy RUTF ☐ Does not favour either ☐ Probably favours standard RUTF ☐ Favours standard RUTF ☐ Varies ☒ Uncertain	No cost-effectiveness analyses done.	
What would be the impact of reduced/no dairy RUTF on equity?		
☐ Increased ☐ Probably increased ☐ No impact ☐ Probably reduced ☐ Reduced ☒ Uncertain ☐ Varies	No studies compared the equity of the intervention with the comparator.	
ACCEPTABILITY **Are the RUTF formulations with reduced/no dairy acceptable to all stakeholders?**		
☐ Yes ☒ Probably yes ☐ No ☐ Probably no ☐ Uncertain ☐ Varies	Four qualitative studies examined the issues of acceptability of RUTF. Similarly, it was noted that the evidence presented did not provide direct comparisons between reduced/no dairy and standard RUTF.	

FEASIBILITY Are the RUTF formulations with reduced/no dairy feasible to produce?		
☒ Yes ☐ Probably yes ☐ No ☐ Probably no ☐ Uncertain ☐ Varies	Seven reports (three qualitative studies, two RCTs and two systematic reviews) discussed the feasibility of alternative RUTF formulations when compared with standard RUTF. Similarly, it was noted that the evidence presented did not provide direct comparisons between reduced/no dairy and standard RUTF.	

SUMMARY OF JUDGMENTS

JUDGMENT							
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Uncertain
BENEFITS	**Trivial**	Small	Moderate	Large		Varies	Uncertain
HARMS	Large	Moderate	Small	Trivial		Varies	**Uncertain**
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES AND PREFERENCES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Uncertain
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST-EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Uncertain**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Uncertain
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Uncertain

RECOMMENDATION

Standard RUTF (with at least 50% of protein coming from dairy products) is recommended for outpatient treatment of children with severe acute malnutrition. Use of RUTF formulations with less than 50% of protein from dairy products for outpatient treatment of children with severe acute malnutrition is encouraged within research and evaluation settings (*conditional recommendation*; *moderate certainty of evidence*).

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	☒	○	○	○

Annex 5.

Guideline development group members

Last name	First name	Gender	Affiliation/City/Country	WHO region	Expertise
Aguilar	Ana Maria	F	Institute of Research on Health and Development Medical College at Universidad Mayor de San Andrés, La Paz, Bolivia	Americas	Management of child undernutrition
Arabi	Ali	M	University of Khartoum, Sudan	Eastern Mediterranean	Paediatrician, management of undernutrition
Briend	Andre	M	Independent, France	Europe	Research in child undernutrition
Hanson	Kerstin	F	Independent, France	Europe	Nutrition programmes
Hossain	Iqbal	M	Nutrition and Clinical Services Division, icddr,b, Bangladesh	South-East Asia	Paediatrics, research in child undernutrition
Jackson	Alan	M	University of Southampton, United Kingdom of Great Britain and Northern Ireland	Europe	Paediatrician, management of undernutrition and child growth
Lewis	Janine	F	Food Standards Australia New Zealand, Australian Capital Territory, Australia	Western Pacific	Food regulation
Maleta	Kenneth	M	University of Malawi College of Medicine, Blantyre, Malawi	Africa	Research in child undernutrition
Manary	Mark	M	Washington University, St Louis, United States of America	Americas	Production and research in RUTF
Venzon Panlilio	Florinda	F	Department of Health, Philippines	Western Pacific	Nutrition programmes, emergencies

Annex 6.
Observers

Last name	First name	Gender	Affiliation/City/Country	Expertise
Carolissen	Verna	F	CODEX/Food and Agriculture Organization of the United Nations (FAO), Rome, Italy	Food standards
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de Pee	Saskia	F	World Food Programme (WFP), Rome, Italy	Nutrition and formulation of foods
de Polnay	Kirrily	F	Médecins sans Frontières (MSF), Brussels, Belgium	Nutrition and Health Adviser
Fleet	Alison	F	UNICEF Supply Division, Copenhagen, Denmark	Technical Specialist (Nutrition)
Guerrero	Saul	M	UNICEF Headquarters, New York, United States of America	Nutrition Specialist
Joannic	Nicola	M	World Food Programme (WFP), Rome, Italy	Nutrition in emergencies
Mates	Emily	F	Emergency Nutrition Network (ENN)	Nutrition emergencies
Oenema	Stineke	F	United Nations System Standing Committee on Nutrition (UNSSCN)	UNSSCN Coordinator
Ranson	Sonia	F	Action Contre Faim (ACF), Brussels, Belgium	Nutrition product quality
Tshitaudzi	Gilbert	M	UNICEF, South Africa	Nutrition policy and programmes
Wilkinson	Caroline	F	UNHCR Division of Operations Services, Geneva, Switzerland	Senior Nutrition Officer, Public Health Section
Xipsiti	Maria	F	Food and Agriculture Organization of the United Nations (FAO), Rome, Italy	Codex Alimentarius

Annex 7.

Systematic review team members

Last name	First name	Gender	Affiliation/City/Country	Topic
Bandsma	Robert	M	University of Toronto, Canada	The efficacy and safety of RUTF containing <50% of proteins coming from dairy products in treating children with uncomplicated severe acute malnutrition
Daniel	Allison	F	University of Toronto, Canada	
Potani	Isabel	F	University of Malawi College of Medicine, Malawi, and University of Toronto, Canada	
Spiegel-Feld	Carolyn	F	University of Toronto, Canada	
Akparibo	Robert	M	Sheffield University, United Kingdom of Great Britain and Northern Ireland	The values, preferences, acceptability, adherence, equity, feasibility, accessibility, sustainability and cost-effectiveness of alternative RUTF formulations
Booth	Andrew	M	Sheffield University, United Kingdom of Great Britain and Northern Ireland	

Annex 8.

Peer reviewers

Last name	First name	Gender	Expertise
de Pee	Saskia	F	Nutrition programmes
Kouanda	Seni	M	Research in treatment of undernutrition
Kumar	Praveen	M	Paediatrics, programmes in management of undernutrition and infectious diseases
Trehan	Indi	M	Research in treatment of undernutrition

Annex 9.

WHO steering committee members

Name	Cluster/Department/Unit	Location
BELTRAN, Filiberto	Nutrition and Food Safety	WHO headquarters, Geneva, Switzerland
BENDABENDA, Jaden	Nutrition and Food Safety	WHO headquarters, Geneva, Switzerland
MONTEZ, Jason	Nutrition and Food Safety	WHO headquarters, Geneva, Switzerland
MURAKAMI, Satoko	Nutrition and Food Safety	WHO headquarters, Geneva, Switzerland
WEISE PRINZO, Zita C.	Nutrition and Food Safety	WHO headquarters, Geneva, Switzerland
ROLLINS, Nigel	Maternal, Newborn, Child and Adolescent Health	WHO headquarters, Geneva, Switzerland
SOLON, Pura	Maternal, Newborn, Child and Adolescent Health	WHO headquarters, Geneva, Switzerland
MARSCHANG, Adelheid	Emergencies	WHO headquarters, Geneva, Switzerland
CAPPELLO, Bernadette	Essential Medicines	WHO headquarters, Geneva, Switzerland
DIOP NDIAYE, Adama	Gender, Equity and Human Rights	WHO headquarters, Geneva, Switzerland
BOISSON, Sophie	Water, Sanitation and Hygiene	WHO headquarters, Geneva, Switzerland
DA SILVA GOMES, Fabio	Nutrition	Pan American Health Organization/WHO Regional Office for the Americas
RODRIGUES DA SILVA BREDA, Joao Joaquim	Noncommunicable Diseases	WHO Regional Office for Europe
UNTORO, Juliawati	Nutrition	WHO Regional Office for the Western Pacific
ONYANGO, Adelheid Werimo	Nutrition	WHO Regional Office for Africa
DE SILVA, Padmini Angela	Nutrition	WHO Regional Office for South-East Asia
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