





Micronutrient status in children aged 6–59 months with severe wasting and/or nutritional edema: implications for nutritional rehabilitation formulations

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Undernutrition remains a global struggle and is associated with almost 45% of deaths in children younger than 5 years. Despite advances in management of severe wasting (though less so for nutritional edema), full and sustained recovery remains elusive. Children with severe wasting and/or nutritional edema (also commonly referred to as severe acute malnutrition and part of the umbrella term “severe malnutrition”) continue to have a high mortality rate. This suggests a likely multifactorial etiology that may include micronutrient deficiency. Micronutrients are currently provided in therapeutic foods at levels based on expert opinion, with few supportive studies of high quality having been conducted. This narrative review looks at the knowledge base on micronutrient deficiencies in children aged 6–59 months who have severe wasting and/or nutritional edema, in addition to highlighting areas where further research is warranted (See “Future Directions” section).

Key words: Severe malnutrition, severe acute malnutrition, severe wasting, nutritional edema, kwashiorkor, marasmus, pediatric, therapeutic feeds, micronutrient status, micronutrient deficiency, micronutrient toxicity, sodium, potassium, calcium, phosphorus, magnesium, iron, copper, zinc, selenium, iodine, thiamine, riboflavin, niacin, pantothenic acid, vitamin B₆, folic acid, vitamin B₁₂, biotin.

INTRODUCTION

Undernutrition remains an important global health burden. It contributes directly or indirectly to 45% of all mortality in children under the age of 5 years.¹ Severe malnutrition is defined broadly as any form of undernutrition associated with a high risk of severe adverse outcomes.² Severe malnutrition is an umbrella term, which, along with stunting (ie, low height for age), underweight (ie, low weight for age) and micronutrient

forms of undernutrition, also includes wasting (ie, low weight for height; also known as marasmus), small mid-upper arm circumference, and nutritional edema (also known as kwashiorkor) manifestations.² The term *severe acute malnutrition* (SAM) is defined in children aged 6–59 months as a weight-for-height z score of less than −3, a mid-upper arm circumference of less than 115mm, and/or the presence of bilateral pitting edema.³ SAM in infants younger than 6 months has different defining parameters, different treatment options, and

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likely different underlying etiology and pathophysiology⁴; SAM in infants is not included in this review. For the purposes of this review, we use the terms *severe malnutrition*, *severe wasting* and/or *nutritional edema*, and SAM interchangeably. Here, we do not discuss the other forms or manifestations of severe malnutrition.

In 2023, the global joint UNICEF, World Health Organization (WHO), World Bank Group estimate of children under the age of 5 years who had severe wasting was 13.7 million.⁵ A large cross-sectional study of 94 low- and middle-income countries (LMICs) that included 804 172 children showed a 14% prevalence of wasting in children younger than 2 years, compared with 9% in children aged 2–4 years.⁶ There are no accurate data on the global prevalence of nutritional edema.⁷ Risk of death is exceptionally high, at 10%–23%, in severely malnourished children during hospitalization^{8–11} but also remains high after discharge.^{9,11} Surviving children also experience lasting consequences such as impaired linear growth, functional deficits, and poor developmental outcomes.^{11–13}

Medically stable children with SAM (also referred to as “uncomplicated” SAM) can be treated in outpatient/community settings with ready-to-use therapeutic food (RUTF). Sick children with SAM (or “complicated” SAM), defined as severe wasting and/or nutritional edema with appetite loss, severe edema, or the presence of medical complications, require inpatient treatment.^{14,15} Treatment first involves stabilization and management of urgent medical conditions. During this stabilization phase, children are fed therapeutic milk F-75 orally or enterally (130 mL/kg/d = ~100 kcal/kg/d).^{15,16} Following stabilization, children are gradually transitioned to high-calorie therapeutic foods, either F-100 and/or RUTF, for their rehabilitation phase (~135–220 kcal/kg/d).¹⁵ Once children are well established with intake of their rehabilitation phase foods, they are discharged home and continue rehabilitation with RUTF.^{14,16}

Micronutrients are essential for health; deficiencies in various micronutrients can have acute and chronic effects on different organ systems in the body.¹⁷ Micro- and macronutrient deficiencies often coexist in severe malnutrition and their effects on morbidity and mortality may be intertwined or compounded. Unfortunately, there are limited high-quality data on the prevalence and degree of severity of micronutrient deficiencies in severely malnourished children.

F-75, F-100, and RUTF all contain micronutrients to potentially prevent or treat deficiencies, reduce the risk of refeeding syndrome, and promote homeostasis.^{14,15,17} The dose of each micronutrient in these therapeutic foods is based largely on expert opinion rather than on direct evidence. The most recent 2013 WHO

recommendations are that supplementation outside of therapeutic feeding can be considered depending on clinical signs and symptoms of overt deficiency.¹⁵

Since their development in the 1990s, there has never been a comprehensive examination of all micronutrients in F-75, F-100, and RUTF, to our knowledge, in relation to requirements for children with SAM throughout the treatment pathway. Although anthropometric recovery is often a metric of successful treatment of SAM, nutritional recovery more broadly including micronutrient status should also be considered. Therefore, determining the appropriate quantity of micronutrients in therapeutic foods is fundamental to understanding how to promote complete nutritional recovery in children with SAM. We assessed the evidence on deficiencies and requirements of specific micronutrients in children with SAM and how the amounts of specific micronutrients added to nutritional rehabilitation formulations compare with their micronutritional needs.

METHODS

To provide a practical understanding of intake of specific micronutrients in children with SAM, we used information published from Nutriset’s website¹⁸ to determine the micronutrient content of standard preparations of F-75, F-100, and RUTF currently formulated (see [Table S1 in the Supporting Information online](#)), and we compared intake to the Dietary Reference Intakes (DRIs). Of note, Nutriset is 1 of more than 20 commercial manufacturers of RUTF,^{19–21} and its RUTF product is commonly used worldwide. Recently, new Codex specifications for RUTF have been published, laying out both minimum and maximum micronutrient constituents of RUTF.²² Nutriset’s RUTF contains micronutrients that lie within these Codex-specified ranges (see [Table S2 in the Supporting Information online](#)). However, it is important to note that Nutriset quotes their stated volumes of constituents are “based on Nutriset’s knowledge of the intrinsic nutrient content of the raw materials and their variability, as well as the variability of the process.”¹⁸ Of note, no Codex specifications exist for F-75 and F-100 formulations.

The DRIs are a set of nutrient-based reference values that can be used to provide guidelines for nutrient intake across the lifespan and are based on both sex and age of healthy individuals. Specifically, the DRIs include the estimated average requirement, the Recommended Daily Allowance (RDA), the Adequate Intake (AI), and the upper limit (UL).^{23,24} Descriptions of each DRI can be found in [Table S3 in the Supporting Information online](#). Although there are limitations to using the DRIs, most notably that they are based on healthy rather

Table 1 Amount and type of therapeutic food prescribed per SAM treatment phase

Age (mo)	Weight (kg)	Phase	Stabilization	Rehabilitation
		Food type	F-75 (75 kcal/100 mL)	F-100 (100 kcal/100 mL) ^a or RUTF (500 kcal/92 g sachet)
		Volume or kcal prescribed per day	130 mL/kg/d (~100 kcal/kg/d) ¹⁵	135–220 kcal/kg ^a 175 kcal/kg/d ^b
6–12	~5 kg ⁹	Estimated intake per day	650 mL	875 mL F-100 or 1.75 sachets RUTF
12–23	~6 kg ⁹		780 mL	1050 mL F-100 or 2.1 sachets RUTF
23–59	~8.5 kg ²⁶		1105 mL	1500 mL F-100 or 3 sachets RUTF

^aF-100 is used in rehabilitation phase for few patients. Note the transition phase (F-100 or RUTF) is not included, because a relatively short duration generally was observed.

^bMidpoint of prescribed amount.

Abbreviations: RUTF, ready-to-eat therapeutic food; SAM, severe acute malnutrition.

than sick populations,²⁴ they were chosen as a universal benchmark to compare intake to recommendations to establish some consistent comparisons. This is in keeping with best practice.²⁵

For some micronutrients, a range of content in Nutriset's therapeutic products F-75 and F-100 is provided due to variability in raw materials and processing, and so the midpoint of these ranges was used for calculations of intake. We then used realistic weights of children based on data from a large international cohort study including infants and children, aged 6–23 months, with severe wasting in Africa and South Asia,⁹ and from a subset of data on children 24–59 months old from a study in Malawi²⁶ to determine average prescriptions for daily intakes of F-75, F-100, and RUTF (Table 1). This allowed us to estimate a realistic daily amount of each micronutrient that a child with SAM would consume across the different phases of treatment and compare it with the RDA or AI and UL of each micronutrient (Figure 1, see Tables S4–S12 in the Supporting Information online).^{27–32} Limited robust methodology data exist on the volumes of therapeutic foods consumed vs the volumes prescribed, though it is generally believed that children infrequently consume the prescribed volumes. One study of 780 children admitted to hospital with SAM reported that 58% children were not able to complete prescribed feedings, with feeding completion defined as consumption of at least 75% prescribed volumes.³³ Therefore, the tables in this review possibly overestimate the percentages of RDAs or AIs consumed for each micronutrient. Additionally, the percentages of RDA or AIs for children with SAM aged 12–23 months were compared with the DRIs developed for healthy children aged 1–3 years. Given the median weight of 6.1 kg is more indicative of an infant younger than 12 months, the percentages of RDA or AI intake may be underestimated. A weight of 8.5 kg was used for volume calculations of children aged 24–59 months.²⁶ The DRIs for this age group were compared with the DRIs for healthy children aged 1–3 years, because 70% of the children 24 months old or older included in the database were younger than

36 months.²⁶ For this reason, the tables provided may overestimate the percentage of RDA or AI micronutrient intake for children aged 36–59 months.

We reviewed the literature by searching the MEDLINE database with the following terms: (“protein-energy malnutrition” or “severe acute malnutrition” or “severe malnutrition” or “kwashiorkor” or “marasmus” or “severe wasting” or “nutritional edema”) AND different variations (“micronutrient X”) of each micronutrient to address questions about 4 key elements of micronutrients and SAM. In addition, the reference list of each included article was evaluated to determine if articles were missed. Articles met inclusion criteria if the study reported on in the article included assessment of micronutrient intake, micronutrient status, or response to nutritional rehabilitation by children with SAM. Articles were excluded if they were not published in the English language or if they were focused on adult populations.

For each micronutrient, we reviewed the following 4 elements: (1) overview of micronutrient: what is the physiological function of micronutrient X in children? How is deficiency or excess of micronutrient X determined? (2) Evidence on the micronutrient status in SAM: what is the evidence on deficiencies and requirements of micronutrient X in children with SAM? (3) Comparison to recommendations: how does the predicted daily intake of micronutrient X in F-75, F-100, and RUTF compare with the DRIs? What are the implications of these levels of intake? And (4) interpretation and discussion: is the content of micronutrient X in F-75, F-100, and RUTF appropriate? Based on the evidence, are there recommendations for further research or revision of formulas or supplementation?

RESULTS

Sodium

Hyponatremia and hypernatremia are generally defined as a serum sodium concentration of less than 135 mmol/L or greater than 150 mmol/L, respectively, with slightly

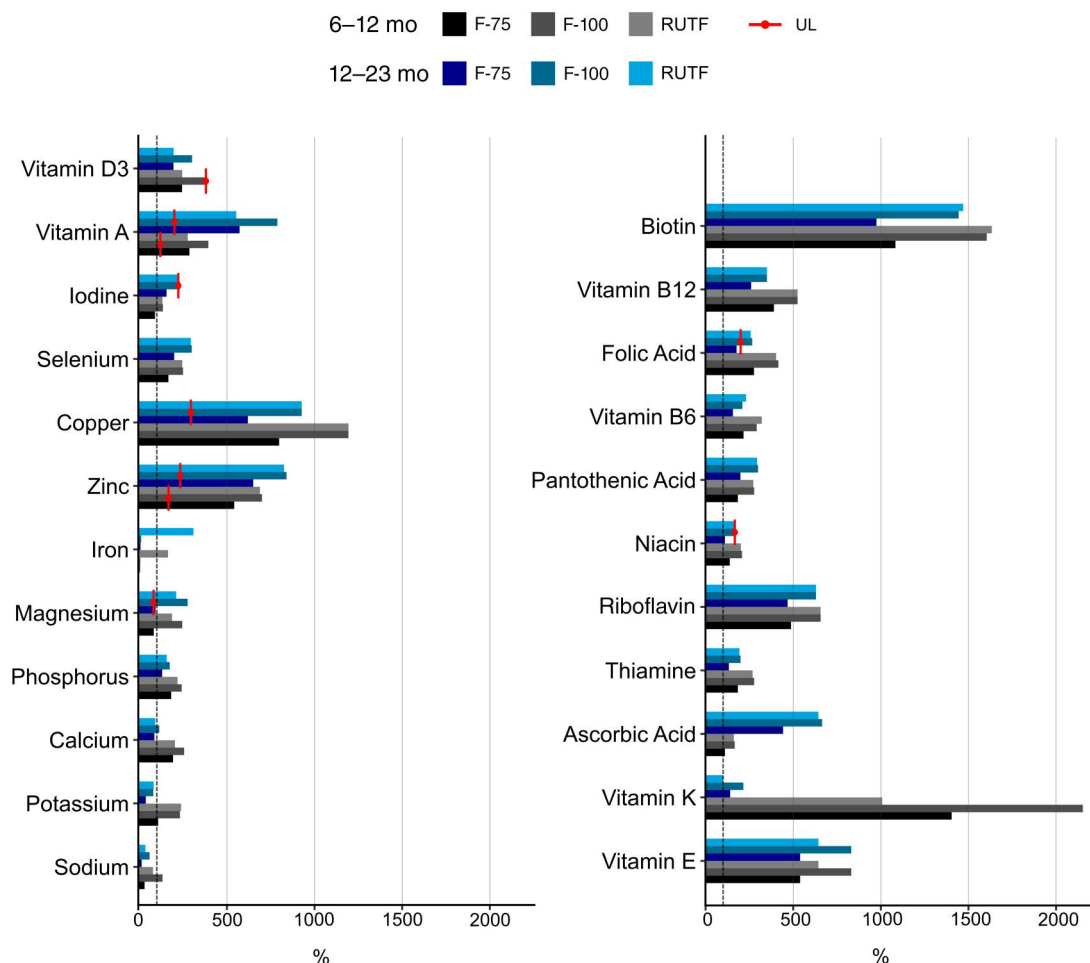


Figure 1 Estimated micronutrient intake as percentage of the Recommended Daily Allowance or Adequate Intake provided for each food type and for age groups 6–12 and 12–23 months. Abbreviation: RUTF, ready-to-eat food.

varying ranges depending on the reporting laboratory.³⁴ Rapid, large changes in sodium levels can lead to cerebral edema characterized by nausea, confusion, seizures, and coma, whereas gradual changes in sodium levels are better tolerated but can lead to vomiting, fatigue, confusion, and headaches.³⁴

Children with SAM are thought to have excess body sodium caused by high intracellular sodium; this perhaps is more pronounced in children with nutritional edema, but supporting evidence is limited.^{35,36} It has been postulated to occur through different adaptive processes. In severe wasting, inhibition and/or slowing of the sodium pump has been reported. In nutritional edema, although an increase in the activity of the Na^+/K^+ -ATPase has been found, leakiness of the cellular membrane is thought to play a role in high intracellular sodium concentrations.³⁷

Children with SAM are more likely to have hyponatremia than are well-nourished children.^{8,38,39} Prevalence of hyponatremia upon admission to hospital for children with complicated SAM has been reported

to be high, ranging from 21% to 52%.^{8,40–42} Some studies have reported higher rates of hyponatremia in children with complicated vs uncomplicated SAM, nutritional edema compared with severe wasting, and, in severe malnutrition, with concurrent diarrhea or pneumonia.^{40,43} Other studies reported similar baseline rates of hyponatremia in complicated and uncomplicated SAM and those with and without diarrhea.^{39,44}

Although hypernatremia has been described in children with SAM, its prevalence is likely lower, ranging from less than 5% to 15% in children with complicated SAM.^{8,40} The Bandsma et al⁸ study of almost 700 children admitted with SAM in Malawi and Kenya showed that the presence of hypo- or hypernatremia did not change significantly after 3 days of F-75 therapy. To our knowledge, no studies have reported on the continued presence or resolution of hypo- or hypernatremia further into the treatment of SAM.

Previously, hyponatremia was shown to be an independent predictor of death, with studies showing a case

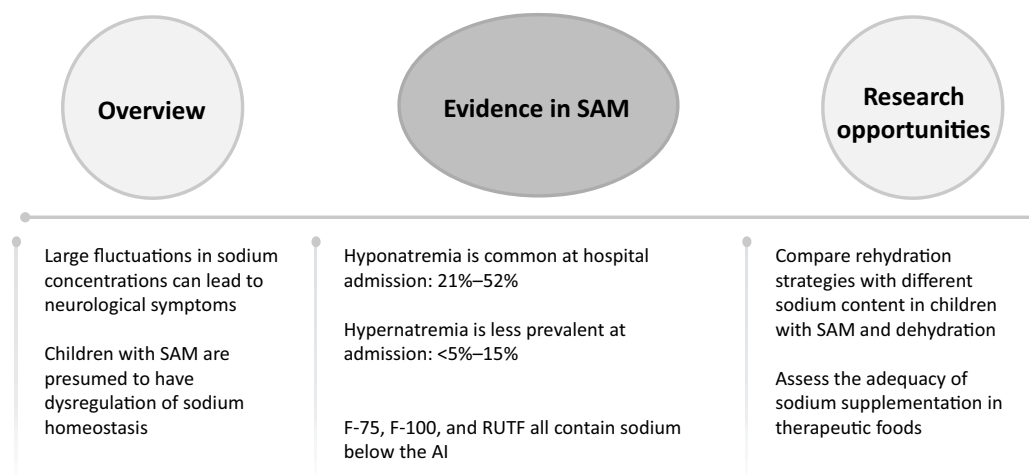


Figure 2 **Sodium take-home messages.** Abbreviations: AI, Adequate Intake; RUTF, ready-to-eat food; SAM, severe acute malnutrition.

fatality rate of 5%–10% in children with diarrhea and hyponatremia.^{45,46} Another study showed the same mortality rates in malnourished children with or without hyponatremia.⁴³ No studies, to our knowledge, have reported on the presence of clinical effects of identified hypo- or hypernatremia specifically in children with SAM. A retrospective study of more than 1200 children under 5 years of age admitted to hospital in Bangladesh showed that children with altered serum sodium levels, including both hypo- and hypernatremia, more often presented with convulsions, altered mental status, dehydration, septic shock, and pneumonia.⁴⁶ In addition, children with hyponatremia were more likely to present at an older age and with SAM.⁴⁶

The major challenge with treating hyponatremia is the widely held belief that treating children with SAM with fluids or foods containing excess sodium may result in increased risk for death, particularly for those with nutritional edema, who are thought to be at risk of cardiac failure and sodium overload.^{36,38,46} WHO recommends a solution known as Rehydration Solution for Malnutrition (ReSoMal) or half-strength, standard, low-osmolarity oral rehydration solution for the treatment of dehydration and diarrhea in complicated SAM and avoidance of using intravenous fluids unless in the setting of shock with severe dehydration.¹⁵ ReSoMal has a sodium content of 45 mmol/L Na, compared with that of the standard WHO low-osmolarity oral rehydration salts, which is 75 mmol/L. The exception to this is in the setting of children with both SAM and cholera or profuse watery diarrhea. These children usually lose high quantities of sodium in their stools and thus should receive the standard WHO low-osmolarity

oral rehydration salts.¹⁵ Recent systematic reviews, though containing small study numbers, considered these universally used oral and intravenous rehydration guidelines as too restrictive, with a lack of evidence to link liberal fluid administration with death or cardiac failure.^{47,48} Other research comparing different rehydration strategies for severe and moderate dehydration is ongoing.⁴⁹

F-75 also has a low concentration of sodium, containing 7.4 mmol/L (<17 mg/100 mL) and providing just 13%–30% of the AI depending on age. F-100 and RUTF, instead, provide 59%–132% and 35%–78%, respectively, of the AI for sodium (Figure 1, see Tables S4–S12 in the Supporting Information online). Given the high prevalence of hyponatremia and low sodium content of F-75, more targeted studies are needed to decipher whether the current sodium content in therapeutic foods is sufficient to deal with the complex nature of sodium dysregulation in children with SAM. See Figure 2 for sodium take home messages.

Potassium

Alteration in serum potassium levels, including both hyper- and hypokalemia, cause hyper- or hypopolarization of the cell, which can result in deadly cardiac arrhythmias (Figure 3).⁵⁰ Hypokalemia is defined as a serum potassium level below 3.4 mEq/L in children or below 4.1 mEq/L in infants. Hyperkalemia is defined as a serum potassium level above 4.7 mEq/L in children or above 5.3 mEq/L in infants.⁵¹

Hypokalemia is a commonly reported electrolyte imbalance in children with SAM, with prevalence rates

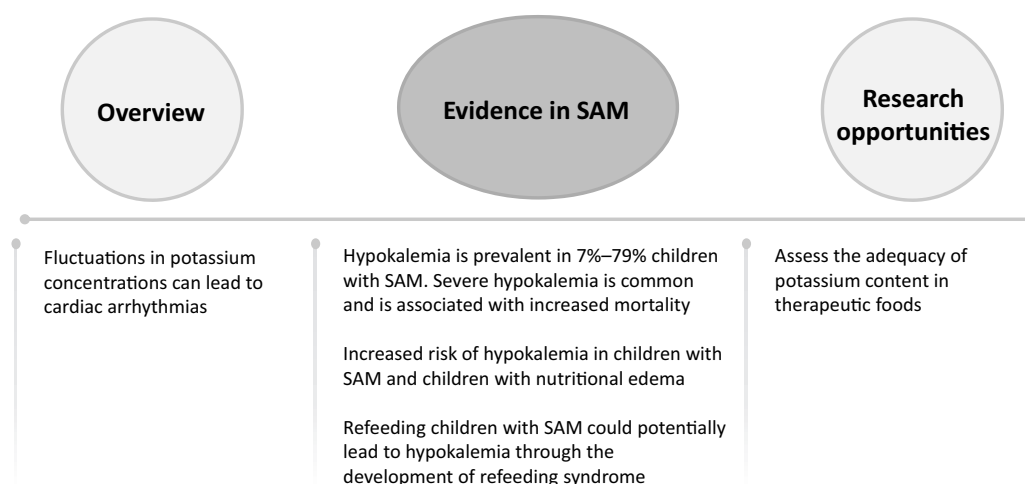


Figure 3 Potassium take-home messages. Abbreviation: SAM, severe acute malnutrition.

varying from 7% to 79% in children with complicated SAM.^{8,41,44,52,53} Only 1 study, to our knowledge, looked at hypokalemia rates between children with complicated (7%; $n = 71$) and uncomplicated SAM (7%; $n = 42$) and found no difference.⁴⁴ Though many studies report on levels of hypokalemia, only 1 study could be identified that reported on hyperkalemia. The study authors reported that 30% of children admitted to hospital with complicated SAM had hyperkalemia, and that increased to 61% after 3 days.⁸ It is important to realize that falsely high potassium concentrations are commonly reported in the context of hemolysis during blood sample collection, so the reported prevalence could be an overestimation. Diarrhea in children with SAM likely increases the risk of hypokalemia,^{39,41,44,54} as does the nutritional edematous rather than the wasting phenotype of SAM.^{40,55} Severe hypokalemia ($<2/5$ mEq/L) is reported in 22%–30% children with SAM at hospital admission,^{52,56} with children often having associated electrocardiogram abnormalities, including T-wave inversion.⁵⁶

Hypokalemia is widely accepted as an important cause of death in children with SAM,^{35,52} with severe hypokalemia reported to have an associated mortality rate of 12%–14%, compared with a mortality rate of 3%–7% in children with normal potassium levels.^{52,53} Though a drop in phosphate level is the hallmark electrolyte change in refeeding syndrome, hypokalemia is also commonly observed. One Kenyan study of 160 children with SAM⁵⁷ reported 21% of children experienced refeeding syndrome; of these, almost half ($n = 16$) had hypokalemia on day 2 of feeding. Hypokalemia persisted on day 7 of feeding in 18%

($n = 3$) of these patients.⁵⁷ A study of 700 children with complicated SAM reported hypokalemia in 23% on admission vs only 4.6% on day 3 of admission.⁸

Current WHO recommendations are that children with SAM and dehydration are treated with low supplementation of sodium and high supplementation of potassium (in the form of ReSoMal), particularly in the setting of diarrhea.¹⁵ This higher concentration of potassium is thought to promote renal excretion of excess sodium and easing of edema⁵⁸ with increasing serum potassium levels. An older study from Malawi showed that children with nutritional edema who were supplemented with high levels of potassium (8 mmol/kg compared with 4 mmol/kg) had lower mortality rates and improved morbidity.⁵⁹ Therapeutic foods provide potassium at varying concentrations. F-75 contains 142 mg/100 mL potassium, providing 37%–107% of the AI, depending on age. F-100 and RUTF have more potassium: 228 mg/100 mL, providing 80%–232% of the AI or 1171 mg/92 g sachet providing 82%–238% of the AI, respectively, depending on age (Figure 1, see Tables S4–S12 in the Supporting Information online). With hypokalemia being common in children with severe malnutrition, it remains unclear whether the amount provided, especially in F-75, is sufficient to restore and maintain normokalemia. See Figure 3 for potassium take-home messages.

Calcium

Calcium is essential for linear growth and also plays a central role in the activation of the immune system in

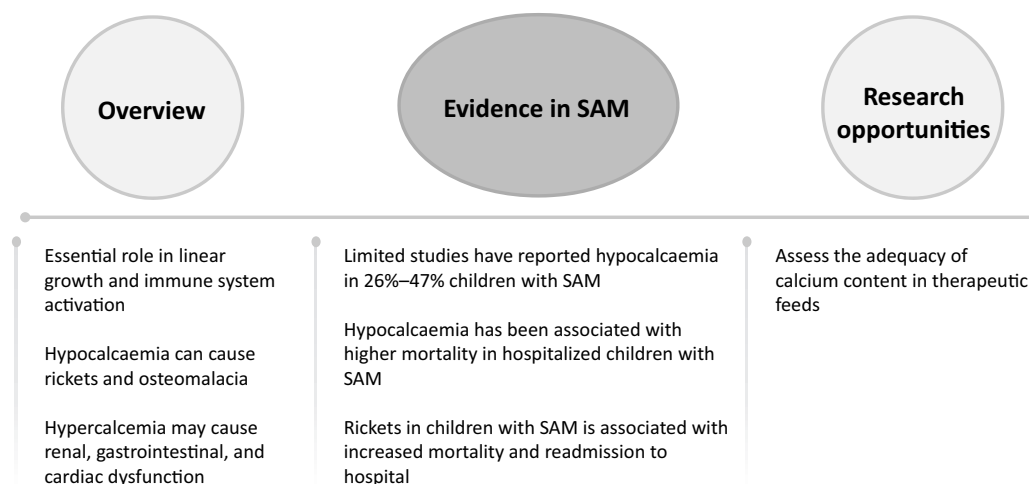


Figure 4 **Calcium take-home messages.** Abbreviation: SAM, severe acute malnutrition.

response to infection. Hypocalcemia is defined as a serum calcium level less than 8.8 mg/dL (2.2 mmol/L) or an ionized calcium level, its biologically active form, of less than 4.6 mg/dL (1.15 mmol/L). Though clinical characteristics of hypocalcemia are often subtle, including increased neuromuscular irritability, 1 main clinical concern is that it can cause rickets and osteomalacia. Hypercalcaemia, which is less common, is defined as a serum calcium level greater than 10.5 mg/dL (2.63 mmol/L) or an ionized calcium level greater than 5.3 mg/dL (1.33 mmol/L).²⁸ Hypercalcaemia can lead to poor muscle tone, renal insufficiency, hypophosphatemia, constipation, nausea, weight loss, fatigue, polyuria, heart arrhythmias, and a higher risk of cardiovascular disease-related death (Figure 4).²⁸

A few cross-sectional studies have reported the prevalence of hypocalcemia in severely malnourished children. Two studies, involving 150 and 333 children, reported hypocalcemia in 26% children admitted with complicated SAM.^{60,61} A smaller study (n = 120) in Nepal found a higher incidence of hypocalcemia in the malnourished group: 47% compared with 7% in the control group.⁶² No data exist on the prevalence of hypercalcaemia in children with severe malnutrition. Hypocalcemia is associated with higher mortality (17%) in hospitalized children with severe malnutrition compared with children without hypocalcemia (5%).⁶⁰ In a study of 150 children with SAM, 42% of children with hypocalcemia had rickets.⁶¹ In a study of 1778 children with severe malnutrition, rickets was associated with increased mortality, any readmission, and readmission for severe pneumonia.⁶³ Although children with SAM

have impaired gut function, their calcium absorption efficiency was reported to be comparable to that of healthy children in 1 study.⁶⁴ A high phytate diet and its inhibitory impact on calcium absorption is an important consideration during the recovery from SAM where RUTF may be supplemented with a largely plant-based diet, a diet common in Africa in particular.⁶⁵ On the other hand, the lactose content in F-75 milk and skim-milk-based RUTF could promote calcium absorption.⁶⁶

F-75, F-100, and RUTF provide up to 86%–193%, 114%–256%, and 91%–203%, respectively, of the calcium AI, depending on the age of the child; however, none of these therapeutic foods exceed the UL (Figure 1, see Tables S4–S12 in the Supporting Information online). No data exist, as far as we are aware, on the resolution or persistence of hypocalcemia after nutritional rehabilitation in children with severe malnutrition. The limited evidence on calcium in children with SAM highlights a gap in current knowledge of calcium adequacy in therapeutic foods. See Figure 4 for calcium take-home messages.

Phosphorus

Phosphate is important for cellular function and bone mineralization (Figure 5). The reference range for normophosphatemia varies with age, and different laboratories quote different ranges on the basis of the assessment technique. Hypophosphatemia, defined in children as a serum phosphate level less than 4.5 mg/dL (1.45 mmol/L),⁵¹ can lead to symptoms ranging from

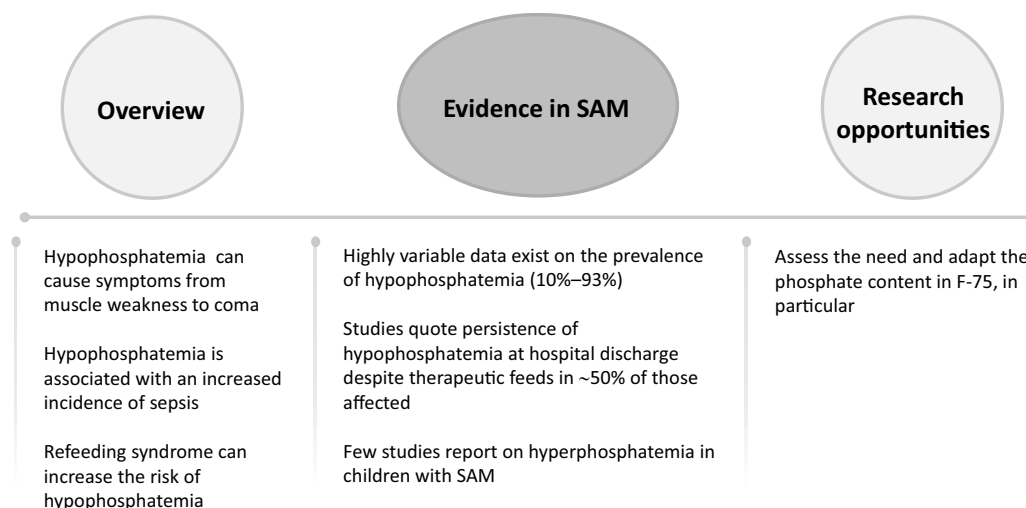


Figure 5 **Phosphorus take-home messages.** Abbreviation: SAM, severe acute malnutrition.

muscle weakness to coma and has been associated with an increased incidence of sepsis.²⁹ Hyperphosphatemia, defined as a serum phosphate level of greater than 6.5 mg/dL (2.1 mmol/L),⁵¹ rarely produces adverse effects in healthy people.²⁹

The reported prevalence of hypophosphatemia among severely malnourished children admitted to hospital varies widely between studies; different definitions of normal cutoffs likely contribute to this. One large study of almost 700 children in Kenya and Malawi reported hypophosphatemia (phosphate < 0.7 mmol/L) in 10% of children admitted with SAM.⁸ This cutoff level is far lower than that used in 4 smaller studies (phosphate range, <1.1 mmol/L to <1.6 mmol/L) reporting rates of 37%–93% in hospitalized cohorts of 48–120 children with SAM.^{67–70} Two of these smaller studies^{67,70} divided hypophosphatemia into mild and moderate-severe categories, with prevalence rates of moderate-severe hypophosphatemia of 20%–25%, closer to that reported by Bandsma et al in Kenya and Malawi.⁸

Hypophosphatemia was associated with the presence of hypothermia, skin manifestations, hypoglycemia, hypocalcemia,⁶⁷ hypomagnesemia, and hypoalbuminemia,⁶⁸ and is common in children with sepsis.⁷⁰ The risk of hypophosphatemia can increase upon the initiation of feedings and onset of refeeding syndrome. Studies reported a fall in serum phosphate levels on days 2 and 3 of feedings, particularly if they are not supplemented with phosphate.^{42,67,71} In a study predating therapeutic foods, authors quoted 3 weeks to regain a normal phosphate level with nonphosphate-

fortified, milk-based diets for malnourished children.⁷² Though levels improve over the course of hospital-based nutritional rehabilitation with F-75 and F-100, hypophosphatemia has been reported to persist in approximately 50% of patients with SAM at discharge from hospital.⁶⁸ However, the mean serum phosphate level at discharge in that study was 1.41,⁶⁸ which, although below the age-specific cutoff for this study, would not be counted as hypophosphatemia in other studies. Bandsma et al⁸ reported the rate of hypophosphatemia in their study of almost 700 severely malnourished children fell from 10% to 5.9% on day 3 of F-75 feeding. Namusoke et al⁶⁹ showed that, with standard nutritional therapy, the mean phosphate level increased from admission through to discharge, with 6% of study participants having persistent hypophosphatemia at discharge and the majority (79%) experiencing their lowest phosphate level at admission. There are far fewer data on hyperphosphatemia in severely malnourished children. One study showed a 30% prevalence of hyperphosphatemia (defined by the authors as >1.5 mmol/L) on admission, which increased to 52% on day 3 of F-75 feeding.⁸

Formulas including F-75, F-100, and RUTF provide approximately 131%–185%, 174%–247%, and 157%–224%, respectively, of the AI for phosphorus, depending on age (Figure 1, see Tables S4–S12 in the Supporting Information online). A summary of the limited data suggests this may be sufficient to prevent clinically relevant hypophosphatemia in most cases. See Figure 5 for phosphorus take-home messages.

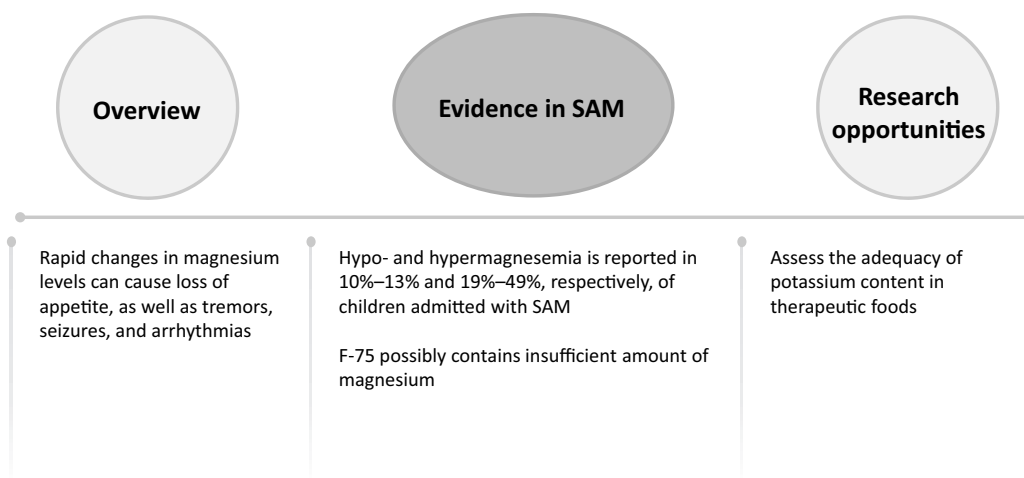


Figure 6 Magnesium take-home messages. Abbreviation: SAM, severe acute malnutrition.

Magnesium

Magnesium is required for more than 300 enzymatic reactions in the body. Hypo- and hypermagnesemia (serum level <0.7 mmol/L and >0.95 mmol/L, respectively) may be asymptomatic or symptomatic. A sudden change in magnesium levels can result in loss of appetite, tremors, seizures, and arrhythmias (Figure 6).⁷³

Varying levels of serum magnesium are found in children with SAM. An Indian study of 43 children reported normal levels upon admission to hospital,⁷⁴ whereas other larger studies, including 72 and 683 severely malnourished children in Africa, reported hypo- and hypermagnesemia in 10%–13% and 19%–49%, respectively, of children admitted with SAM.^{8,68} An Ethiopian study of 72 children admitted to hospital with SAM showed that admission serum phosphate levels were positively associated with serum magnesium levels, and both were strongly positively correlated with serum albumin levels.⁶⁸ No significant difference was found between children with or without edema.⁶⁸

F-75, F-100, and RUTF are all fortified with magnesium, providing 82%–131%, 245%–393%, and 187%–300%, respectively, of the AI or RDA for magnesium (Figure 1, see Tables S4–S12 in the Supporting Information online). The effect of these therapeutic foods on magnesium levels varies in different studies. A large study of 683 children with SAM reported rates of hypomagnesemia and hypermagnesemia at admission were 10% and 19%, respectively, which changed after 3 days of F-75 therapy to 17% and 9.8%, respectively.⁸ This study would suggest additional magnesium may be required in F-75 to maintain a normal magnesium status. However,

a smaller ($n = 72$), though longer, study showed that when F-75 or diluted F-100 (used due to inadequate F-75 stock) was administered to patients with SAM, a subsequent increase in magnesium occurred, with all patients having normal or high (83%) concentrations of magnesium at discharge from hospital, indicating sufficient supplementation.⁶⁸ An additional study investigating the effect of combined intramuscular (day 1) and oral magnesium (days 2–14) supplementation on top of therapeutic feedings in 50 children with SAM in India found a reduction in magnesium level from admission to discharge, though all levels were within the normal range.⁷⁴ More studies are required to determine the adequate magnesium dose in therapeutic foods, in particular, F-75. See Figure 6 for magnesium take-home messages.

Iron

Iron is a central component of hemoglobin and red blood cell production, and is involved in many enzymatic reactions. The main concern with iron deficiency is the development of iron deficiency anemia (IDA). Anemia, defined as a hemoglobin concentration of less than 110 g/L (severe anemia, <70 g/L), can lead to fatigue, weakness, difficulty concentrating, and impaired immune function and may cause irreversible growth and cognitive delays if left untreated.⁷⁵ Though the prevalence of IDA has declined slightly worldwide over the past 25 years, it continues to affect close to 300 million children, mostly in LMICs where SAM is also highly prevalent (Figure 7).^{75,76}

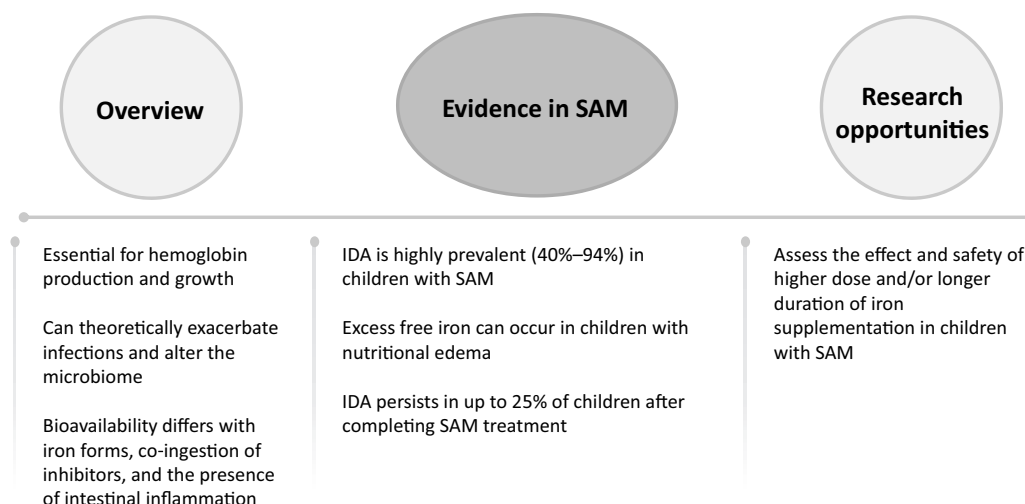


Figure 7 Iron take-home messages. Abbreviations: IDA, iron deficiency anemia; SAM, severe acute malnutrition.

Several studies have reported that children with SAM present with high rates of IDA. In a cohort of 801 children in Burkina Faso, IDA rates on admission were 40%,⁷⁷ and higher rates were observed in multiple smaller trials conducted in Malawi and India, with sample sizes of 389 (48% IDA), 131 (67% IDA), and 50 (94% IDA) children with SAM.^{78–80} Additionally, 2 of these studies reported that 25%–46% of patients had anemia categorized as severe^{79,80} and required transfusion.⁷⁹ Conversely, some studies found that children with nutritional edema present with increased serum free iron, compared with children with wasting or not, and researchers have suggested this represents iron overload.^{81–85}

Currently, F-75 contains very low levels of iron, providing between 4% and 9% of the RDA (Figure 1, See Tables S4–S6 in the Supporting Information online). Given that F-75 is provided for stabilization in the early stages of treatment, this is likely appropriate because iron supplementation, theoretically, may exacerbate infections⁸⁶; thus, low iron doses may mitigate this risk. However, F-100 also provides considerably low amounts of iron, meeting only 6%–15% of the RDA, despite its role in rehabilitation (Figure 1, See Tables S7–S9 in the Supporting Information online). Although most patients will also only use F-100 for a short time, those with concurrent SAM and swallowing dysfunction, such as patients with cerebral palsy, may require F-100 for the duration of their rehabilitation. On the other hand, RUTF contains much higher amounts of iron and provides between 163% and 441% of the RDA (Figure 1, See Tables S10–S12 in the

Supporting Information online). Although this may seem excessive, iron needs are likely increased due to increased growth velocity.⁷⁷ Additionally, although most children with SAM complete treatment within 6–8 weeks, IDA likely remains prevalent, with rates reported to be 21%–25% among children discharged from treatment despite meeting growth requirements for discharge.^{77,78} One study compared 2 alternative, plant-based RUTF products with lower concentrations of cow's milk (0% and 9% milk) than standard RUTF (28% milk) and showed considerably lower rates of IDA upon completion of treatment of the plant-based RUTF (12%–18% vs 25% in those receiving standard RUTF).⁷⁸ The authors attributed the improvement in IDA rates to the lower amount or absence of cow's milk in the recipes and subsequent improved bioavailability of iron and reduction of potential iron inhibitors, namely, calcium, whey, and casein.⁷⁸ However, other experts have also noted the considerably higher amounts of iron (non-heme compared with heme iron in standard RUTF) in the alternative RUTF products (35.1 mg/100 g in 0% milk and 31.6 mg/100g in 9% milk) compared with standard RUTF (10.5 mg/100g).^{77,82}

It is possible that malnutrition-associated enteropathy and inflammation may upregulate the regulatory protein hepcidin, thereby decreasing iron absorption from the enterocyte by trapping the iron in the enterocyte, as has been shown in inflammatory bowel disease and other conditions.^{87,88} For this reason, higher-dose enteral iron supplementation may not result in increased iron levels until inflammation is controlled; instead, intravenous iron supplementation or longer durations

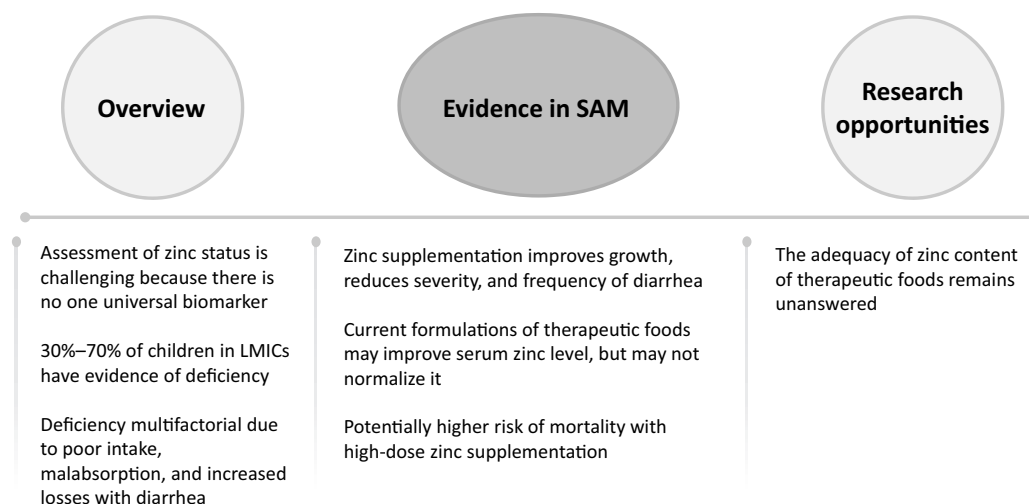


Figure 8 Zinc take-home messages. Abbreviations: LMIC, lower- and middle-income country; SAM, severe acute malnutrition.

rather than higher doses of enteral iron supplementation may be physiologically better therapeutic options.⁸⁹

Interestingly, novel nano-iron supplements have recently been shown to improve iron stores while reducing moderate-severe diarrhea compared with standard ferrous sulphate iron supplements.⁹⁰ These supplements may be a potential treatment consideration in the future. It may be valuable to explore whether increased amounts of iron in F-100, and possibly RUTF; improvement in bioavailability of iron; longer duration of iron supplementation beyond standard nutritional therapy; or intravenous iron supplementation could lead to improvement in iron status in children recovering from SAM. However, these efforts must be balanced with the potential risks of additional iron, including possible negative effects on the microbiota, impacts on growth (particularly in iron-replete children), impairment of cognitive development, and increased gastrointestinal side effects resulting in nonadherence and interference with absorption of other trace elements.^{77,86} See Figure 7 for iron take-home messages.

Zinc

Clinical features of zinc deficiency include poor appetite, growth failures, skin lesions, diarrhea, poor wound healing, and impaired immune response. Assessment of zinc status is challenging given that there is not 1 widely accepted sensitive and specific biomarker of zinc status, and zinc status is affected by multiple factors, including the acute-phase response in infection.⁹¹ The prevalence of zinc deficiency is estimated to include 30%–70% of

children in LMICs and is likely related to a combination of factors, including poor intake, malabsorption, or increased losses due to diarrhea (Figure 8).^{92–95} Multiple studies have shown that children with malnutrition had significantly lower levels of serum zinc than did healthy children.^{95–97} Studies have indicated clinical benefits of zinc supplementation, such as improved growth and reduction of both acute and chronic diarrhea.^{98–101} WHO advises 14 days of supplemental zinc at 20 mg/d for children with acute diarrhea to reduce diarrhea frequency and severity.¹⁰²

Current SAM treatment protocols provide between 16 and 36 mg/d zinc depending on the phase of treatment and age (Figure 1, see Tables S4–S12 in the Supporting Information online). This exceeds the UL for zinc in all cases (5–7 mg/d depending on age). However, it should be noted that the UL for zinc has also been criticized for being too low,¹⁰³ and it has been suggested that zinc requirements for children in LMICs may be increased because of the high levels of phytate in cereal-based diets and the poor access to meats and shellfish.⁹⁴ A study in India reported that a combined supplemental antioxidant (zinc dose not reported) for 30 days significantly increased and normalized serum zinc levels in malnourished children, though it must be noted their nutritional intake was otherwise not commented upon.⁹⁷ One study involving 12 patients with SAM in Bolivia¹⁰⁴ found that serum zinc status improved on the WHO SAM protocol, but that it may take up to 30 days of treatment before normalization of serum zinc levels. It is notable that up to 25% of the patients in that study did not have improvements in serum zinc status,¹⁰⁴

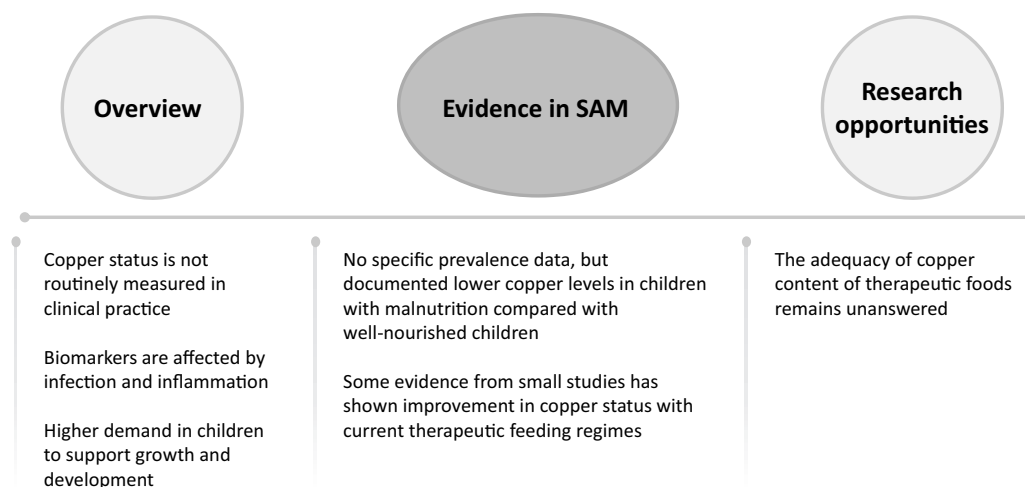


Figure 9 Copper take-home messages. Abbreviation: SAM, severe acute malnutrition.

suggesting insufficient supplementation in therapeutic food products. However, higher doses of zinc supplementation (6 mg/kg/d) started early in treatment (day 1 of admission) and lasting for 15–30 days have been linked to higher rates of mortality than in children receiving lower doses of supplementation (1.5 mg/kg/d = 7.5–12.75 mg/d).¹⁰⁵ It is thought that the initiation of high doses of zinc during stabilization may have harmful effects on the immune response during sepsis and affect absorption of other micronutrients.^{105,106} More investigation into the optimal intake of zinc in children with SAM is warranted. See Figure 8 for zinc take-home messages.

Copper

Copper status is not routinely assessed in clinical practice, and the available biomarkers (serum copper and ceruloplasmin) to assess status can be influenced by other factors, such as infection and inflammation (Figure 9).¹⁰⁷ In children and infants, the demand for dietary copper is higher than in adults for their development and growth.¹⁰⁸

Copper deficiency may lead to the development of muscle numbness, burning, optic neuropathy, fatigue, weakness, IDA, metabolic syndrome, and increased risk of infection. Copper toxicity is rare in individuals who do not have a hereditary copper homeostasis defect but can lead to liver disease, gastrointestinal symptoms, hemolytic anemia, anuria, and central nervous system symptoms, such as motor and cognitive abnormalities.³²

As with other trace elements, children with malnutrition are at risk of acquired copper deficiency. Several studies based on cohorts from India (n = 117),⁹⁵ Bangladesh (n = 120 and n = 68),^{96,109} Turkey (n = 32),¹¹⁰ Egypt (n = 68),⁸¹ Morocco (n = 36),¹¹¹ and Tanzania (n = 50)¹¹² documented lower copper levels in severely malnourished children compared with healthy, well-nourished children. One study in India reported copper deficiency only in malnourished children with marked linear growth retardation.¹¹³ Therapeutic foods contain high amounts of copper and exceed the UL in all products for children older than 1 year (Figure 1, see Tables S4–S12 in the Supporting Information online). There is no UL available for younger children; however, all products exceed the AI for this age group. Small studies in South Africa (n = 22) and Bolivia (n = 12) showed that WHO nutritional therapy could return serum copper and ceruloplasmin levels to normal within 15 days¹⁰⁴ to 30 days,¹¹⁴ together with significant weight gain.¹¹⁴ Neither toxic levels nor adverse events were reported in these studies.^{104,114} In summary, there are some small, underpowered studies that suggest that current amounts of copper provided in therapeutic foods are sufficient to address copper deficiency in severely malnourished children. However, larger scale studies would be required to verify this. See Figure 9 for copper take-home messages.

Selenium

Selenium is fundamental for human health through its antioxidant properties to prevent oxidative damage by free radicals and its role in the production and

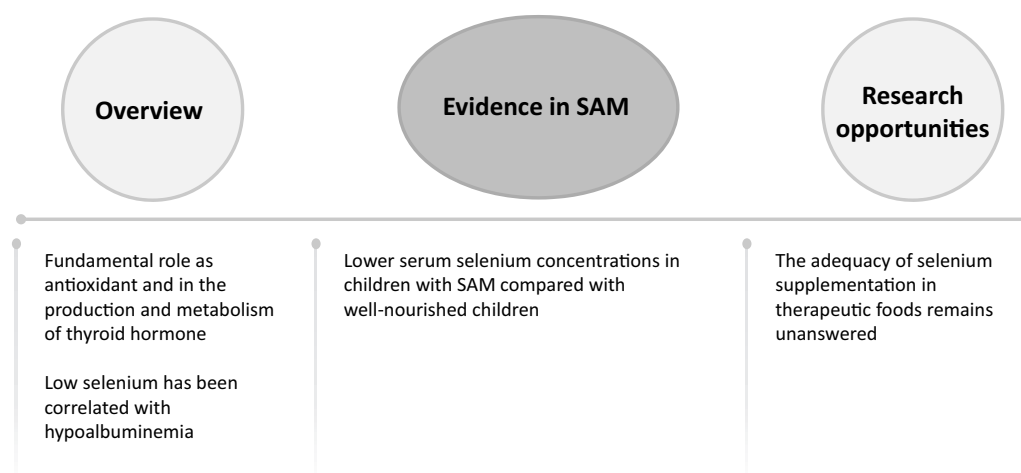


Figure 10 **Selenium take-home messages.** Abbreviation: SAM, severe acute malnutrition.

metabolism of thyroid hormone (Figure 10). Selenium status is generally reported as concentration in serum, which is indicative of recent selenium intake, whereas hair or nail selenium levels are better indicators of longer-term intake over months to years.³⁰ It is worth noting that a study in infants showed a correlation between low selenium levels and hypoalbuminemia, recommending both levels be assessed when interpreting possible deficiency.¹¹⁵ Selenium deficiency presents clinically in the form of cardiomyopathies (Keshan disease), skeletal muscle myopathies (Kashin–Beck disease), and microcytic anemia. Growth retardation and alopecia with pseudoalbinism are early clinical symptoms of deficiency in infants, which are reversible with adequate amounts of selenium intake.¹¹⁶

Previous theories of a causative association between oxidative stress and the edematous phenotype of SAM¹¹⁷ were refuted in a double-blind, randomized controlled trial (RCT; $n = 2372$) in Malawi in which daily high-dose antioxidant supplementation including selenium for 5 months did not prevent the onset of nutritional edema in children.¹¹⁸ Multiple studies in Egypt ($n = 68$), Morocco ($n = 160$), South America ($n = 43$), Sudan ($n = 53$), and Turkey ($n = 32$) found that lower serum selenium concentrations were present in children with nutritional edema compared with children who had severe wasting and in children with severe malnutrition compared with healthy, well-nourished children from the same communities.^{81,110,111,114,119–121}

Studies looking at the outcomes of selenium deficiency in children with SAM are sparse. One study of more than 500 children in Ethiopia found that selenium

deficiency (measured by serum levels of selenium) was associated with lower scores for all cognitive outcomes on the Wechsler Preschool and Primary Scale of Intelligence and a 25-item school-readiness test, compared normal serum selenium levels in children.¹²² There was no significant difference in selenium level between children with stunting and those without stunting. However, it was reported that children with coexisting stunting, anemia, iron deficiency, and selenium deficiency scored significantly lower on these cognitive tests than those without these burdens.¹²² Selenium content in F-75, F-100, and RUTF is approximately 1.6–4.3 times greater than the AI or RDA for children aged 6–59 months; however, it is below the UL for each age group (Figure 1, see Tables S4–S12 in the Supporting Information online). A small study in 1992 showed that milk intervention in children aged 5–48 months ($n = 22$) with nutritional edema improved plasma selenium concentration from baseline but not to levels of well-nourished healthy community control participants ($n = 22$) at 30 days of refeeding.¹¹⁴ Interestingly, a study of 160 children with SAM in Egypt showed resolution of selenium deficiency at the end of WHO-recommended nutritional therapy for all neurotypical children, though deficiency persisted for a large proportion of children with both SAM and cerebral palsy.¹¹⁹ The result of selenium supplementation on developmental outcomes in children with SAM has not been assessed in controlled trials, to our knowledge. Although no direct evidence exists, it is possible that selenium deficiency is common in children with severe malnutrition and may be improved during nutritional

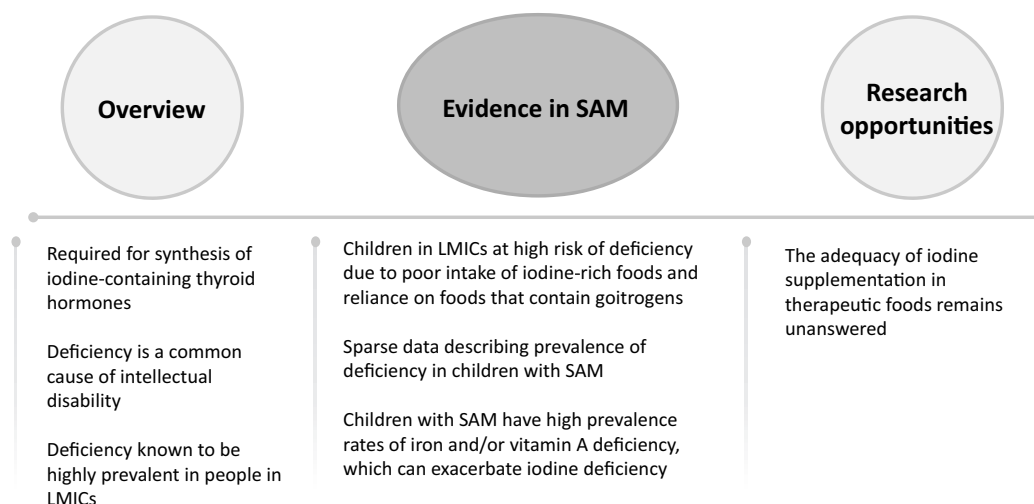


Figure 11 **Iodine take-home messages.** Abbreviations: LMIC, lower- and middle-income country; SAM, severe acute malnutrition.

rehabilitation with WHO-recommended therapies; however, it remains unclear if the deficiency is fully corrected with these approaches. See Figure 10 for selenium take-home messages.

Iodine

Iodine is required for the synthesis of iodine-containing thyroid hormones, thereby helping in the regulation of the basal metabolic rate. Iodine deficiency is considered a common cause of intellectual disability and can lead to cognitive and motor impairments (Figure 11). A clinical sign of iodine deficiency is the development of a goiter.^{30,123} Iodine status is biochemically measured using urinary concentrations of iodine, with below 100 µg/L considered to be inadequate and below 20 µg/L considered severely deficient.^{30,123,124}

Iodine deficiency is highly prevalent among people in LMICs, affecting 1.88 billion people worldwide, including 241 million school-aged children, with many regions considered to have endemic iodine deficiency.¹²⁵ Many children in LMICs are at increased risk of developing iodine deficiency due to poor intake of iodine-rich foods and the reliance on food that contain goitrogens, such as soy, cassava, and cruciferous vegetables, which may exacerbate iodine deficiency.^{30,124,126} For these reasons, the risk of iodine deficiency for children with SAM is likely high; however, there are little to no data describing prevalence of iodine status in this population. Some small studies (n = 12–68) suggest that intestinal dysfunction in children with SAM may contribute to malabsorption of iodine.^{127–130} To our

knowledge, however, there are no reports on urinary iodine concentrations in these children. Additionally, children with SAM high prevalence rates of iron and/or vitamin A deficiency (VAD), which are also known to exacerbate iodine deficiency.^{30,124,126}

The current F-75 content of iodine is 90% and 220% of the AI and RDA for children aged 6–12 months and 12–23 months, respectively; whereas F-100 and RUTF both provide higher amounts: 135% and 333% (F-100) and 132% and 327% (RUTF). It must be noted that the iodine content of both F-100 and RUTF exceed the UL recommended for children older than 1 year (the UL is not established for children 6–12 months old) (Figure 1, see Tables S4–S12 in the Supporting Information online). In other populations, it has been shown that providing supplemental iodine can be associated with transient hyperthyroidism¹²⁴; however this has not been explored in children with SAM, despite intakes exceeding the UL with standard nutritional therapy. Given the importance of iodine on cognitive development, it may be valuable to assess prevalence of iodine deficiency in children with SAM and subsequent response to therapeutic feedings. See Figure 11 for iodine take-home messages.

Vitamin A

Vitamin A is essential in growth, reproduction, immunity, vision, and, more broadly, cellular differentiation and proliferation (Figure 12).¹³¹ The main clinical manifestations of VAD are xerophthalmia and increased susceptibility to severe infection. Systemic vitamin A

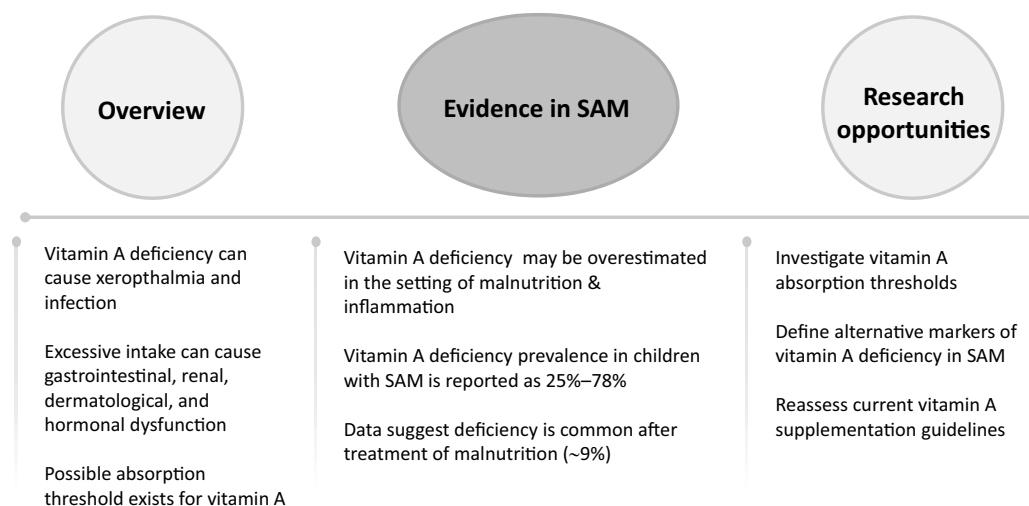


Figure 12 **Vitamin A take-home messages.** Abbreviation: SAM, severe acute malnutrition.

toxicity can be due to acute or chronic excessive ingestion, and its effects include altered mucocutaneous abnormalities, headaches, nausea, vomiting, skin irritation, and reversible hypothyroidism and renal dysfunction. The adverse effects seen with single high-dose vitamin A supplementation are usually mild and transient, and include nausea, vomiting, headaches (in older children), and bulging fontanelles (in younger children).¹³²

VAD is commonly defined as plasma or serum retinol concentration or retinol binding protein (RBP) level less than 0.70 $\mu\text{mol/L}$.¹³³ However, serum retinol levels only reflect liver vitamin A stores when they are extremely depleted or high. Additionally, RBP, which is produced by the liver, can be reduced in malnutrition and inflammation, thereby overestimating VAD.¹³⁴ Liver vitamin A reserves, a better reflection of subclinical VAD, can be measured indirectly with a relative dose-response test, but this is more time consuming and costly.¹³⁵ The prevalence of VAD globally has reduced from 39% to 30% over the past 2 decades (1991–2013) with little to no improvement in the prevalence levels seen in sub-Saharan Africa and South Asia. A pooled analysis of population-based studies estimated approximately 94 500 deaths due to diarrhea and 11 200 deaths due to pneumonia were attributed to VAD globally in 2013, accounting for 1.7% of all deaths in children younger than 5 years in LMICs.¹³⁶ WHO recommends periodic supplementation in areas with high prevalence of night blindness or VAD and acutely in the setting of measles.¹³²

Current WHO recommendations for vitamin A supplementation in children with SAM are ~5000 IU/

1500 μg retinol activity equivalent vitamin A daily (1 IU retinol = 0.3 μg retinol activity equivalent), either as an integral part of therapeutic foods or as part of a multi-micronutrient formulation.¹⁵ F-75, F-100, and RUTF provide 286%–810%, 394%–1125%, and 277%–790% of the AI and RDA requirements for vitamin A, respectively, depending on age, and contain 2.3–5.6 times the reported daily UL, depending on the age group (Figure 1, see Tables S4–S12 in the Supporting Information online).

VAD in children with SAM has been reported to range from 25% to 78%,^{77,137,138} though many of these studies did not correct the retinol or RBP level for inflammation. A recent study in Burkina Faso noted 25% of children with uncomplicated SAM had VAD, with levels corrected for inflammation, when admitted to their nutrition program. This percentage decreased to 9% after an average of 2 months of nutritional treatment.⁷⁷ Interestingly, in this study,⁷⁷ researchers compared the effects of reduced-dose RUTF with standard dosing (anything from a 10% to ~50% reduction in RUTF dose with an equivalent reduction in vitamin A supplementation) and found no difference in VAD between the reduced and standard RUTF dosing groups at the end of the treatment period.⁷⁷ A study in Bangladesh, looking at the safety of a single high dose (200 000 IU) of vitamin A in conjunction with daily low dose (5000 IU) vitamin A in comparison with standard low-dose vitamin A (5000 IU) in children with SAM and diarrhea or lower respiratory tract infection found no difference in efficacy or safety over the 15-day study period.¹³⁸ Though the RBP levels may have been

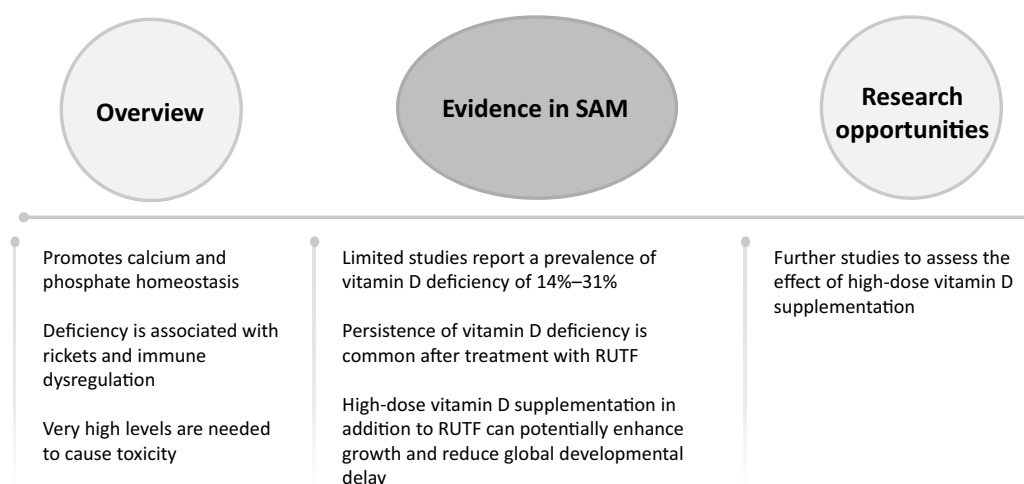


Figure 13 Vitamin D take-home messages. Abbreviation: SAM, severe acute malnutrition.

confounded by a concordant country-wide biannual vitamin A supplementation in the Burkina Faso study,⁷⁷ both studies raise questions about possible vitamin A absorption thresholds, vitamin A liver reserves, the appropriateness of using retinol or RBP as a marker of VAD in children with SAM and the possible need for continued micronutrient supplementation after nutritional therapy is completed. More research into these questions is needed before changes to dosing guidelines can be safely made. See Figure 12 for vitamin A take-home messages.

Vitamin D

The main function of vitamin D in the body is promoting calcium and phosphate homeostasis, thereby helping to maintain skeletal health and prevent rickets in children (Figure 13). Vitamin D deficiency is also associated with adverse respiratory outcomes in asthma exacerbations and tuberculosis reactivation, likely due to an effect on the immune system.¹³⁹ Vitamin D status is indicated by serum levels of 25-(OH)D, though variation in levels exist depending on the assay used.¹⁴⁰ Though there is no consensus on the optimal level of vitamin D to maintain good bone health, the most commonly used definitions consider concentrations greater than 50 nmol/L (>20 ng/mL) to be normal, 30–50 nmol/L (12–20 ng/mL) to be insufficient, and less than 30 nmol/L (<12 ng/mL) to be deficient.¹⁴¹ The level for vitamin D toxicity is considered to be greater than 375 nmol/L (>150 ng/mL).¹⁴² Vitamin D toxicity in children is rare but reported among patients taking very

high doses of vitamin D. Its adverse effects are attributed to hypercalcemia and include nausea, vomiting, muscle weakness, neuropsychiatric disturbances, polyuria, excessive thirst, and kidney stones.¹⁴³

Though data are scant, a recent review of worldwide vitamin D status suggests widespread vitamin D deficiency, with the highest prevalence in Asia, the Middle East, and Africa. The prevalence of vitamin D deficiency in malnourished children reported in the literature varies widely, from 14% to 31% in children with SAM or moderate acute malnutrition in 2 studies in Africa^{144,145} to 65% in children with SAM reported in a study in India.⁶¹ Though immunoassay methods were used to determine 25-(OH)D level in each of these studies, they differed in their definition of deficiency. The reported prevalence of rickets in children with SAM also differs in studies, ranging from 13% in a Kenyan study⁶³ to 42% in an Indian study.⁶¹ Importantly, 1 group in Kenya showed an association between rickets in this population cohort, with an increased risk of mortality, hospital readmission, and readmission with pneumonia.⁶³

F-75, F-100, and RUTF therapeutic feedings provide 195%–276%, 301%–430%, and 196%–280%, respectively, of the RDA for vitamin D (Figure 1, see Tables S4–S12 in the Supporting Information online). There is a lack of studies evaluating the exact effect of nutritional treatment of SAM on vitamin D levels. One RCT in Pakistan¹⁴⁶ of high-dose vitamin D₃ (2 oral doses of vitamin D₃ 200 000 IU at weeks 2 and 4) in addition to RUTF (600 IU/sachet) in children with SAM found increased weight-for-height or for length z score, increased weight, and reduced rate of global

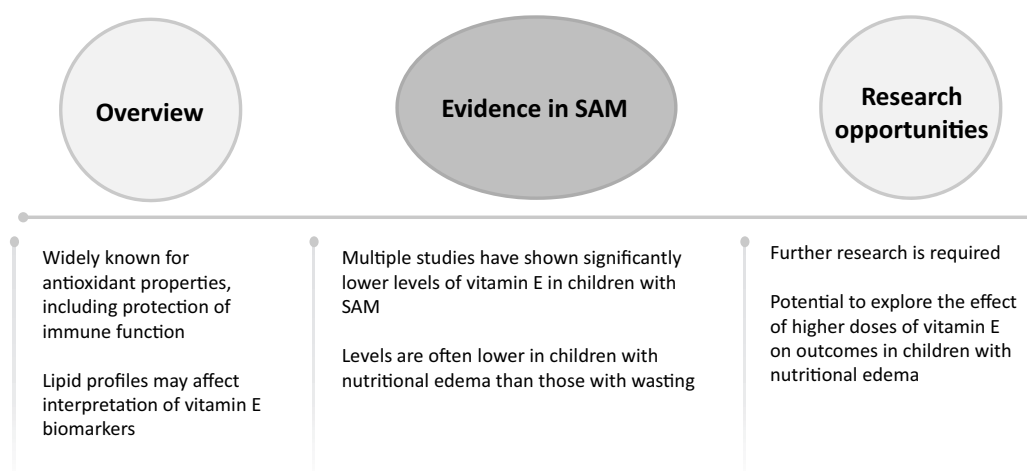


Figure 14 **Vitamin E take-home messages.** Abbreviation: SAM, severe acute malnutrition.

development delay vs RUTF alone. All patients who received additional high-dose vitamin D had normal (>50 nmol/L) 25-(OH)D levels at week 8 (study end) in comparison with only 42% of those treated with RUTF alone. Of note, 27% of patients who received additional high-dose vitamin D had levels exceeding 125 nmol/L but less than 250 nmol/L, and no adverse effects or hypercalcemia were detected.¹⁴⁶ A larger phase 2 RCT in Pakistan is currently underway aiming to show weight gain (primary outcome) and enhanced neurodevelopment, muscle mass accumulation, resolution of systemic inflammation, and antimicrobial immune function (secondary outcomes) in children with SAM supplemented with high-dose vitamin D.¹⁴⁷ The results of this study could help guide whether an increased dose of vitamin D supplementation for children diagnosed with SAM is warranted, as expected. See Figure 13 for vitamin D take-home messages.

Vitamin E

Vitamin E is widely known for its antioxidant properties (Figure 14). It protects immune function by serving as an oxidant scavenger and protecting cells from free-radical damage.^{148,149} Deficiency has been linked to spinocerebellar ataxia, skeletal myopathy, retinopathy, and anemia.^{30,148} Determination of deficiency is challenging given that plasma levels are affected by confounding factors such as age, sex, and lipid profiles, which may be altered in the context of SAM.¹⁴⁸ Because α -tocopherol levels are highly correlated with blood lipid levels, ratios of α -tocopherol to plasma lipids are often considered

more accurate measures of vitamin E status. However, both of these measures may produce unreliable results.¹⁴⁸

Multiple studies have shown that children with SAM have both significantly lower serum vitamin E levels and lower α -tocopherol to lipid ratios.^{81,97,150–153} Importantly, these levels are often lower in children with nutritional edema than in those with wasting.^{81,151} Vitamin E deficiency has been proposed as a potential factor in the onset of nutritional edema.¹¹⁷ Golden and Ramdath¹¹⁷ proposed that nutritional edema results from a leakage in the vascular system when antioxidant activity is not sufficient to neutralize free-radical damage produced by the inflammatory response. However, in a 2005 study, high-dose vitamin E supplementation in 2372 children (given in an antioxidant complex also containing riboflavin, selenium, and *N*-acetylcysteine) in rural Malawi did not improve the likelihood of developing nutritional edema, compared with placebo.¹¹⁸

Specifically, F-75, F-100, and RUTF provide 540%–764%, 831%–1187%, and 644%–920%, respectively, of the AI or RDA for vitamin E (Figure 1, see Tables S4–S12 in the Supporting Information online). These supplementation doses clearly exceed the AI or RDA for all age groups but remain far below the UL. However, given the findings that children with nutritional edema typically have lower levels of biomarkers of vitamin E circulating and that these lower levels have the potential to be related to poor immune function, it is worth further investigation to determine if higher doses of supplemental vitamin E in therapeutic feeding regimes would improve the outcomes in children with SAM, particularly nutritional edema. See Figure 14 for vitamin E take-home messages.

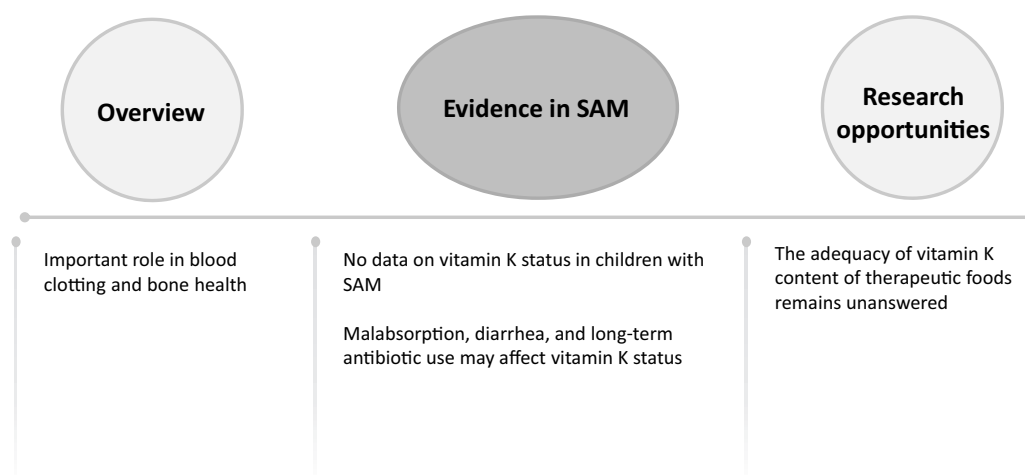


Figure 15 **Vitamin K take-home messages.** Abbreviation: SAM, severe acute malnutrition.

Vitamin K

Vitamin K status has an important role in blood clotting, and deficiency typically presents with a vitamin K-responsive increase in prothrombin time and, in severe cases, a hemorrhagic event. Vitamin K also plays a role in bone health, including bone mineralization and turnover (Figure 15).

To our knowledge, there are no dedicated data on vitamin K status (namely, intake, requirements, and rates of deficiency) in children with SAM. However, it is well known that malabsorption, diarrhea, and long-term antibiotic use (>10 days) may affect vitamin K status.^{32,154} One study in India assessed vitamin K status of sick children (n = 120) receiving long-term antibiotic therapy and found a trend in children with severe malnutrition toward increased prothrombin time compared with children with no or moderate malnutrition.¹⁵⁴ The same study showed that providing a prophylactic dose of vitamin K (0.5 mg/kg to a maximum of 10 mg) on day 1 of antibiotic therapy did not mitigate this effect, indicating factors other than vitamin K deficiency are important.¹⁵⁴ It is standard practice to initiate antibiotics in children with SAM, which may affect vitamin K status and prothrombin time, but there is limited evidence on this relationship in this population.

F-75, F-100, and RUTF provide 140%–1404%, 215%–2153%, and 101%–1008%, respectively, of the AI or RDA for vitamin K depending on the age of the child (Figure 1, see Tables S4–S12 in the Supporting Information online). No UL is reported for infants and children aged less than 3 years. These high levels may help prevent the development or exacerbation of

deficiency during SAM treatment. More studies are required to assess the status of vitamin K in children with SAM and rates of vitamin K deficiency with antibiotic therapy in this population. See Figure 15 for vitamin K take-home messages.

Ascorbic acid

Ascorbic acid, more commonly known as vitamin C, is essential for immune function, collagen synthesis, and development of the nervous system, and is also a cofactor for enzymatic reactions (Figure 16).^{155,156} Deficiency can present as scurvy, which is characterized by gingival swelling, corkscrew and swan-neck hair formation, fatigue, muscle pain, joint pain, and bleeding.³⁰ It can also present with anemia, hypocholesterolemia, and hypoalbuminemia.³⁰ Vitamin C deficiency is diagnosed by serum or plasma levels below 0.2 mg/dL ascorbic acid (the reduced form of vitamin C), though these levels can be affected by recent dietary intake.¹⁵⁷ A more accurate measure of deficiency is leukocyte ascorbic acid (<8 mg/dL is considered deficient), which is reflective of tissue stores.¹⁵⁸ However, leukocyte levels can be reduced in certain disease states, including asthma and diabetes, and both serum and leukocyte ascorbic acid levels can be reduced in infection and stress. It is recommended that both levels be measured when assessing vitamin C status.¹⁵⁹

Both intestinal barrier dysfunction and oxidative stress seen in children with SAM have been postulated to contribute to vitamin C deficiency.^{81,160} Little is known about vitamin C status in children with SAM.

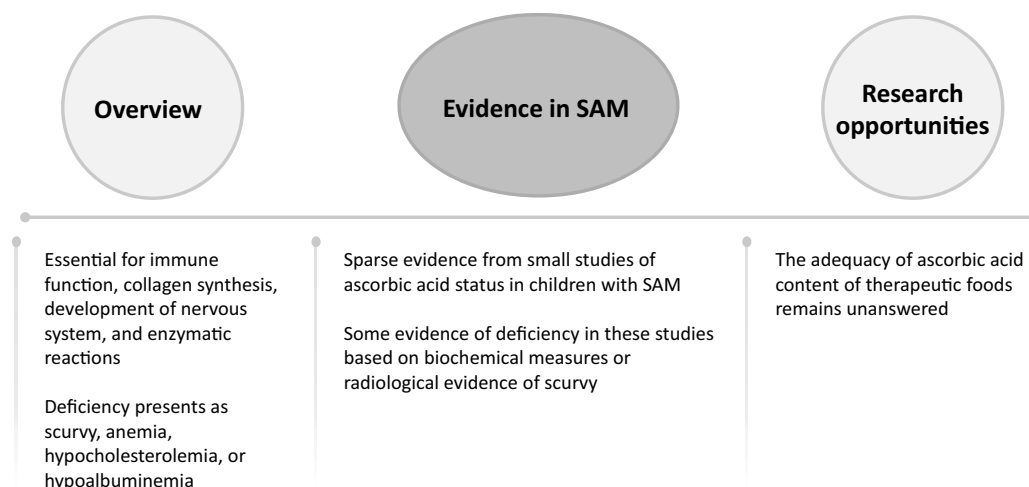


Figure 16 Ascorbic acid take-home messages. Abbreviation: SAM, severe acute malnutrition.

One small study ($n = 26$) in Nigeria reported similar but low leukocyte ascorbic acid levels (8–15 mg/dL) in children with SAM and healthy children.¹⁶¹ A study of 50 children with SAM in India found that 96% of the children had radiological evidence of vitamin C deficiency,¹⁶² though another Indian study reported that only 5% of children with SAM had cutaneous symptoms of vitamin C deficiency.¹⁶³ F-75, F-100, and RUTF provide 111%–626%, 166%–950%, and 161%–920%, respectively, of the vitamin C AI or RDA; however, none of these therapeutic foods exceeds the UL (Figure 1, see Tables S4–S12 in the Supporting Information online). More studies are needed to ascertain the vitamin C status in severely malnourished children and decipher if the current supplementation in therapeutic foods is safe and adequate. See Figure 16 for ascorbic acid take-home messages.

Thiamine

Thiamine (vitamin B₁) is an essential nutrient that plays a role in many cellular processes, including carbohydrate and amino acid catabolism (Figure 17). Signs of deficiency include anorexia, weight loss, cognitive changes, muscle weakness, and cardiovascular effects.³¹ Thiamine is only available through exogenous sources, and depletion of stores can occur in 2 weeks.¹⁶⁴ Refeeding syndrome may also cause the onset of thiamine deficiency because rapid nutritional rehabilitation increases thiamine turnover.¹⁶⁴ Children in LMICs, particularly children with SAM, are at high risk of deficiency for several reasons, including their reliance on

refined processed cereals or tubers (eg, rice, wheat, cassava), poor intestinal absorptive capacity, and enteropathy.^{31,164,165} Toxic effects have not been demonstrated with higher doses of thiamine.^{31,165} For this reason, it has been recommended to treat patients at risk of refeeding syndrome with high doses of thiamine (recommended range: 1–2 mg/kg/d to 100–300 mg/d) to prevent the onset of thiamine deficiency with the provision of nutrition.^{166–168}

Studies in Ghana ($n = 146$) and Jamaica ($n = 25$) have indicated a prevalence of 40% of children with SAM having moderate to severe thiamine deficiency upon hospital admission.^{169,170} Furthermore, the Ghanaian study indicated that deficiency resolved in children who were treated with 2.5 mg/d thiamine.¹⁷⁰ Currently, F-75 provides between 0.55 and 0.94 mg/d, which is significantly lower than the recommendations cited above for refeeding risk (Figure 1, see Tables S4–S6 in the Supporting Information online). Hiffler et al^{164,165} cited the low risk of side effects with high doses of thiamine, the high prevalence of thiamine deficiency in children with SAM, and the potential to improve outcomes with higher doses of thiamine during stabilization as rationales for increasing the amount of thiamine in F-75 from 0.085 mg/100 mL to 7.5 mg/100 mL, which would provide patients between 50 and 80 mg/d thiamine. Furthermore, given that thiamine stores are directly related to recent intake, children with SAM may benefit from higher doses of thiamine in both F-100 and RUTF than what is currently provided. F-100 and RUTF provide between 0.1 and 1.4 mg/d, depending on age (Figure 1, see Tables S7–S12 in the

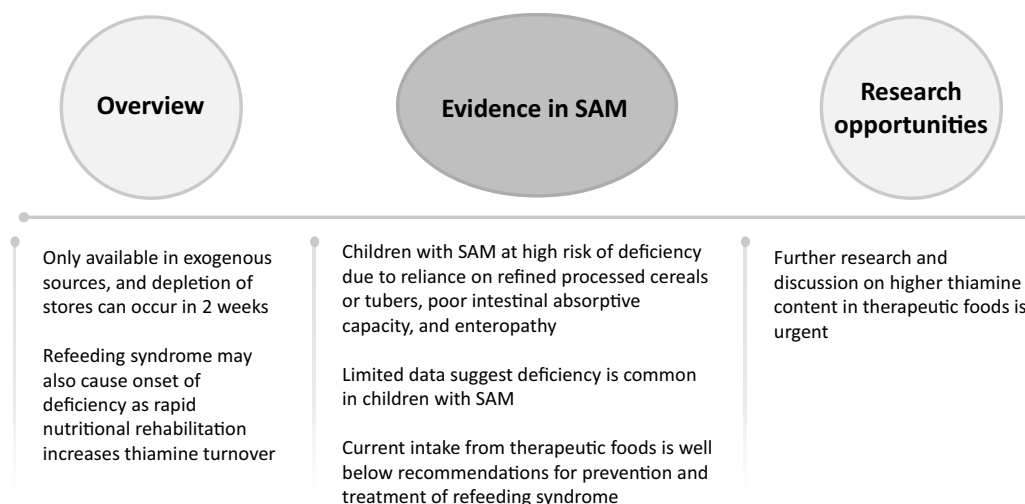


Figure 17 **Thiamine take-home messages.** Abbreviation: SAM, severe acute malnutrition.

Supporting Information online). It has been suggested that 5–10 mg/d during nutritional rehabilitation would be appropriate.¹⁶⁴ Additionally, F-100 and RUTF could be increased to 1.0 mg/100 mL and 4.5 mg/92 g, respectively, to provide the recommended 1–2 mg/kg/d for children.^{164,166} The current evidence strongly supports that research and discussion on providing a higher content of thiamine in therapeutic foods are urgent. See Figure 17 for thiamine take-home messages.

Riboflavin

Riboflavin (vitamin B₂) is an essential component of 2 coenzymes, flavin mononucleotide (FMN) and flavin adenine (FAD) that are involved in cell metabolism and energy production (Figure 18). Deficiency of riboflavin typically occurs in conjunction with other nutritional deficiencies, and symptoms of deficiency may include skin disorders, sore throat, increased blood volume, glossitis, angular stomatitis, and anemia.^{31,123} Riboflavin deficiency is determined by measuring concentrations of coenzymes FMN and FAD or by measuring erythrocyte glutathione reductase activity coefficient (EGRAC), which is a ratio of erythrocyte glutathione reductase activity in the presence of FAD to that without added FAD. A ratio greater than 1.4 indicates riboflavin deficiency.³¹

Evidence of riboflavin status in children with SAM is sparse. Three small studies reported no evidence of riboflavin deficiency at presentation in children with SAM. However, 1 study in Nigeria noted that although children with SAM (n = 44) did not have evidence of riboflavin deficiency based on EGRAC, control study

participants (n = 23) did.¹⁷¹ This finding could be related to muscle breakdown releasing FAD, which can normalize intracellular FAD levels, including in erythrocytes.^{171,172} Additionally, a study from western Africa¹⁷³ examined riboflavin status of 60 malnourished children in relation to thyroid hormones and urinary excretion of organic acids. The researchers found that although plasma FAD and FMN did not indicate global riboflavin deficiency, the synthesis of mitochondrial riboflavin cofactors was reduced in children with SAM compared with control participants.¹⁷³ They explained this by attributing low levels of the thyroid hormone T3 in children with malnutrition as a contributor to reduced enzymatic activity responsible for the conversion of riboflavin to its cofactors.¹⁷³

Current formulations of F-75, F-100, and RUTF provide well over the AI for riboflavin, at 468%–663%, 630%–900%, and 630%–900%, respectively, of the AI, equating to an intake of 1.95–3.2 mg/d (Figure 1, see Tables S4–S12 in the Supporting Information online). No UL has been established for riboflavin; its absorption is reported to be saturated in adults at doses exceeding 27 mg, and excess amounts are excreted in the urine.³¹ Current available data are not conclusive to suggest that a change in riboflavin supplementation for children with SAM is warranted. See Figure 18 for riboflavin take-home messages.

Niacin

Niacin (vitamin B₃) is an essential nutrient involved in many cellular functions, including oxidative stress regulation, mitochondrial homeostasis, autophagy, and gene

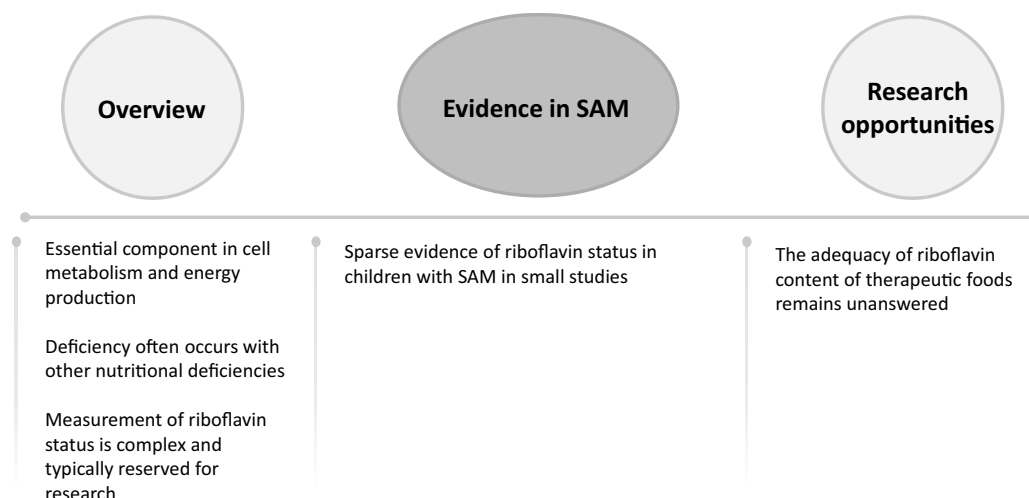


Figure 18 Riboflavin take-home messages. Abbreviation: SAM, severe acute malnutrition.

expression regulation (Figure 19).^{174–176} In addition to dietary sources, niacin can also be generated in the liver from the amino acid tryptophan,^{31,176,177} which requires adequate levels of iron, vitamin B₆, and riboflavin.^{31,178,179} Severe deficiency of niacin can lead to pellagra, which presents with dermatitis, dementia, diarrhea, and ultimately, death.^{31,123,180} Niacin status is ideally measured through urinary excretion of niacin metabolism products N¹-methylnicotinamide and 2-pyridone, with a combined excretion of less than 1.5 mg/24 hours indicative of severe deficiency.¹²³ Excess niacin intake, in the form of nicotinic acid (>1500 mg/d in adults) or nicotinamide (>3000 mg/d in adults), can lead to flushing, gastrointestinal upset, hepatotoxicity, and glucose intolerance. These levels are far in excess of the UL for adults (35 mg/d), but case reports and clinical trials have reported flushing effects at doses of 30–1000 mg/d resulting in withdrawal from treatment.^{31,123}

There currently are no direct data on niacin status in children with SAM. However, niacin deficiency has been commonly reported in regions where maize is a large component of the diet^{180,181} and is thought to reduce niacin's absorption.¹⁸² A prospective analysis of food and nutrient intakes by 1651 children at risk of nutritional edema in Malawi showed that although there was a substantially deficient intake of niacin in all children, there was no difference in intake between those who developed nutritional edema and those who did not.¹⁸³ Children with SAM have a high prevalence of iron deficiency,^{77,78} which may affect endogenous niacin production. Furthermore, children with complicated SAM have lower serum tryptophan levels than children

with stunting and control participants without stunting,¹⁸⁴ which also could affect endogenous niacin production.

Current formulations of therapeutic foods contain between 111% and 237% of the AI or RDA for niacin, with F-100 and RUTF just reaching the UL for children older than 1 year and exceeding it for those older than 2 years (Figure 1, see Tables S4–S12 in the Supporting Information online). In absolute terms, this provides 3.2–14.3 mg/d (UL 10 mg/d). Niacin doses recommended for pellagra treatment in children and adolescents are 50–300 mg/d.¹⁸⁵ More data on niacin status in children with SAM are required to make recommendations on niacin content in therapeutic foods. See Figure 19 for niacin take-home messages.

Pantothenic acid

Pantothenic acid (vitamin B₅) is an essential micronutrient needed for the synthesis of coenzyme A and acyl carrier protein, which are required for the metabolism of lipids (Figure 20).^{186,187} Deficiency of pantothenic acid often occurs in conjunction with other micronutrient deficiencies, making it difficult to determine clinical signs of deficiency.¹⁸⁸ Signs of deficiency may include numbness and burning of the hands and feet, headache, fatigue, irritability, restlessness, poor sleep, and gastrointestinal disturbances.³¹ Pantothenic acid status can be measured in blood, urine, or tissue samples, but urinary excretion is most closely related to dietary intake.³¹

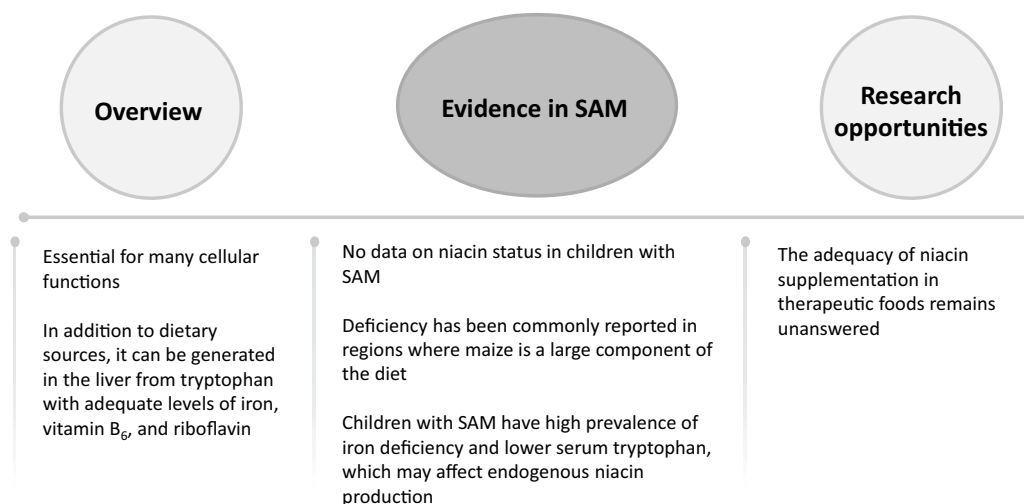


Figure 19 Niacin take-home messages. Abbreviation: SAM, severe acute malnutrition.

There currently appear to be no data on intake, requirements, or prevalence of deficiency of pantothenic acid in children with SAM. Current therapeutic foods contain between 184% and 427% of the AI for children (Figure 1, see Tables S4–S12 in the Supporting Information online). No UL for pantothenic acids is reported. There is no evidence on pantothenic acid status in children with SAM to assess the appropriateness of this amount. Studies are warranted to determine the prevalence of deficiency and establish the optimal supplementation of pantothenic acid in this population. See Figure 20 for pantothenic acid take-home messages.

Vitamin B₆

Vitamin B₆, also known as pyridoxine, acts as a cofactor for more than 100 enzymatic reactions, most of which are involved with protein metabolism, including tryptophan metabolism.^{27,189} Vitamin B₆ also plays a role in cognitive development, glucose metabolism, immune function, and hemoglobin formation (Figure 21).²⁷ Isolated vitamin B₆ deficiency is rare but may present in conjunction with other micronutrient deficiencies and is associated with microcytic anemia, dermatitis, glossitis, weakened immune function, and neurological changes.³¹ Vitamin B₆ status can be determined by measuring concentrations of pyridoxal 5'-phosphate (a B₆ active coenzyme form); total vitamin B₆ in plasma, erythrocytes, or urine; or by measuring tryptophan metabolites.³¹

We found no recent data on vitamin B₆ status in children with SAM. One study published in 1961

showed that in a small sample of children with nutritional edema (n = 13), all had evidence of B₆ deficiency by measure of urinary tryptophan metabolites.¹⁹⁰

Current therapeutic foods provide between 156% and 330% of the RDA for vitamin B₆, which is equivalent to 0.65–1.65 mg/d (Figure 1, see Tables S4–S12 in the Supporting Information online). Treatment guidelines for vitamin B₆ deficiency in children and adolescents suggest doses between 5 and 25 mg/d for 3 weeks, followed by 2.5–5 mg/d.¹⁹¹ Research is needed to ascertain the prevalence of vitamin B₆ deficiency in children with SAM and to determine whether current micronutrient supplementation in therapeutic foods is optimal. See Figure 21 for vitamin B₆ take-home messages.

Folic acid

Folic acid, or folate, is important for the formation of red blood cells and certain amino acids, especially methionine. Folic acid deficiency can present clinically with weight loss, growth delay, and megaloblastic anemia.³¹ Severe folate deficiency can also result in diarrhea, cognitive impairment, and behavioral disorders (Figure 22).³¹ Isolated folate deficiency is uncommon; it often coexists with other micronutrient deficiencies. Folic acid status is typically measured using serum folate, with less than 3 ng/mL considered deficient. However, serum folate is reflective of recent dietary intake, whereas erythrocyte folate concentrations are considered a better marker of longer-term folate status. An erythrocyte folate concentration less than 140 ng/mL is considered deficient.³¹

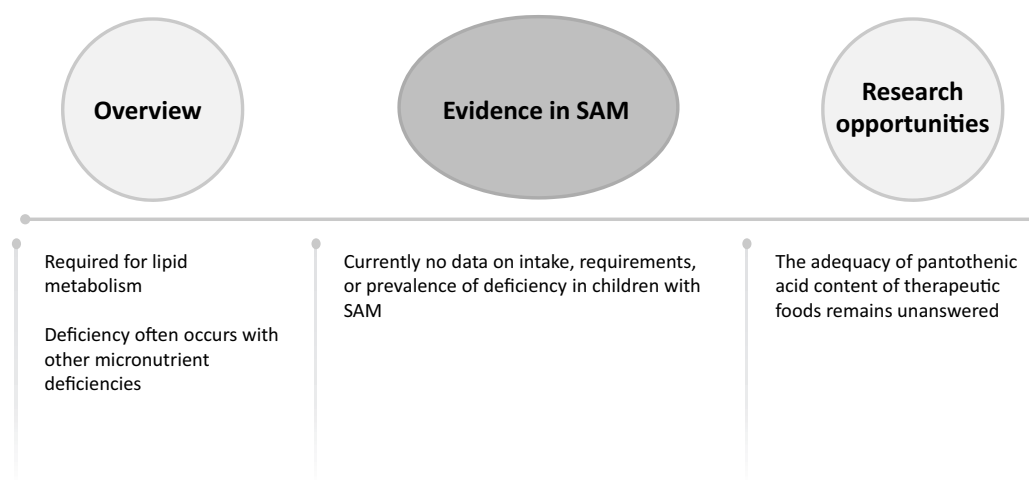


Figure 20 Pantothenic acid take-home messages. Abbreviation: SAM, severe acute malnutrition.

As with many other micronutrients, data on folic acid status in children with SAM are based on small studies, with only a few studies having been published recently. Prevalence of deficiency has been reported to be between 0% and 70%,^{79,80,172,192,193} with the majority of reports ranging between 3% and 20%.^{79,80,193} The high variability in prevalence rates has been attributed to geographic variability in dietary intake or supplemental folic acid provided to pregnant and lactating women.^{80,172,193} High rates of breastfeeding have been associated with low prevalence of folate deficiency. Folate levels in breast milk are known to be consistent regardless of maternal stores,^{194,195} which may contribute to lower rates of folate deficiency. One small study of children with SAM ($n = 48$) in South Africa noted a high prevalence (67%) of biochemical folate deficiency (measured by serum folate) among those patients who died ($n = 6$) compared with a lower prevalence of deficiency (14%) among those who survived.¹⁹⁶ Additionally, a correlation with supplemental folic acid (dose not specified) and recovery from SAM was noted among 253 children with complicated SAM in Ethiopia.¹⁹⁷

The previous 2003 WHO guidelines recommended 5 mg of supplemental folic acid on day 1 of treatment for complicated SAM and 1 mg/d thereafter in addition to the therapeutic feedings.¹⁶ However, the most recent 2013 WHO guidelines do not recommend any supplementary folic acid to what is currently in therapeutic foods,¹⁵ which provide between 221 and 570 $\mu\text{g/d}$ folic acid (Figure 1, see Tables S4–S12 in the Supporting Information online). These estimated intakes for both

F-100 and RUTF are above the UL set for children older than 12 months (300 $\mu\text{g/d}$). Given the high rates of deficiency noted in children with SAM, these high doses may be warranted. See Figure 22 for folic acid take-home messages.

Vitamin B₁₂

Vitamin B₁₂ (cobalamin) functions as a coenzyme important for cellular metabolism, especially for DNA synthesis, energy metabolism, and conversion of homocysteine to methionine.¹⁹⁸ In children, B₁₂ deficiency can lead to anemia, neurological complications such as impaired motor and cognitive functions, as well as delays in growth and neurodevelopment (Figure 23).³¹ Vitamin B₁₂ status is typically measured using serum B₁₂, with levels less than 148 pmol/L considered deficient.¹⁹⁹ However more sensitive markers of B₁₂ status include serum methylmalonic acid and homocysteine levels.³¹

B₁₂ deficiency can occur for a number of reasons. B₁₂ is not present in plants; therefore, low intake of animal products or fortified foods can lead to B₁₂ deficiency.³¹ Gastrointestinal factors also play a crucial role in determining B₁₂ status. The absorption of B₁₂ from food is a complex process that requires the proper production of intrinsic factor, stomach acid, and functioning of the gut. Gastrointestinal conditions, such as atrophic gastritis, *Helicobacter pylori* infection, and small-intestine bacterial overgrowth, are associated with malabsorption of B₁₂.^{200–202}

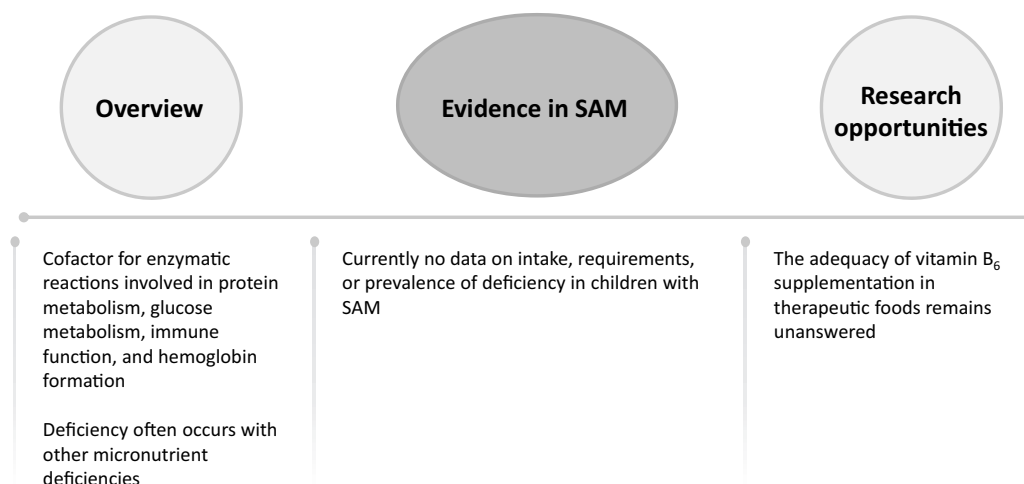


Figure 21 Vitamin B₆ take-home messages. Abbreviation: SAM, severe acute malnutrition.

Two small studies ($n = 50$ and $n = 48$) in India reported a high prevalence (range, 34%–58%) of vitamin B₁₂ deficiency in children with SAM.^{80,203} However, the findings in these reports of relatively high prevalence of B₁₂ deficiency are in contrast to other studies. A larger study in India ($n = 131$) showed that although 30.5% of children with SAM had megaloblastic anemia, only 6.1% had deficient serum B₁₂ levels.⁷⁹ Other studies have shown normal or elevated serum B₁₂ levels in children with SAM.^{193,204,205} One of these older studies, from 1983,²⁰⁵ ($n = 34$) also noted that patients with nutritional edema had higher serum B₁₂ levels than did children with severe wasting.²⁰⁵ It has been suggested that higher or normal levels of serum B₁₂ in malnourished children do not necessarily indicate adequacy, but rather that binding capacity of B₁₂ in the liver is limited due to fatty infiltrates, particularly in nutritional edema, leading to higher serum levels. Some authors also correlated high serum B₁₂ levels with decreased liver function²⁰⁵ and with bacterial overgrowth in the gut.²⁰⁶ Children with SAM have evidence of bacterial overgrowth, which may be influencing serum B₁₂ measurements.^{207–210} Given the reliance on plant-based foods in diets in most LMICs, it is not surprising that children with SAM would be at risk of B₁₂ deficiency. Moreover, comorbidities prevalent in SAM, like malaria, human immunodeficiency virus, and tuberculosis, have also been implicated as risk factors for B₁₂ deficiency.^{211,212}

Most treatment guidelines suggest using intramuscular B₁₂ injections to treat severe deficiencies, which is not always a feasible solution for LMICs. Current

therapeutic foods provide between 260% and 525% of the RDA for vitamin B₁₂, which translates to a dose of 1.95–4.5 $\mu\text{g}/\text{d}$ (Figure 1, see Tables S4–S12 in the Supporting Information online). Although these doses may exceed the RDA, there is no UL reported for vitamin B₁₂, and recent evidence suggests that much higher doses (1000 μg) of oral vitamin B₁₂ taken for 4 months may be required to address diet-related deficiencies in children under 2 years of age.²¹³ Given the low risk associated with high doses of vitamin B₁₂ and that a UL has not been set for vitamin B₁₂, it may be valuable to increase the amount provided in therapeutic foods. However, research with a more sensitive marker of B₁₂ status, such as serum methylmalonic acid, may be required to better understand prevalence of deficiency. See Figure 23 for vitamin B₁₂ take-home messages.

Biotin

Biotin is absorbed in the small intestine and serves as a cofactor for different carboxylases, which play an essential role in the metabolism of glucose, fatty acids, and amino acids (Figure 24).^{31,214} Additionally, it is an important component of gene regulation and cell signaling.^{31,215} Clinical manifestations of deficiency are nonspecific and include periorificial dermatitis, hair loss, neurological dysfunction, and metabolic abnormalities.^{31,216} Indicators of biotin deficiency include low serum and low urinary levels of biotin, high urinary excretion of 3-hydroxyisovaleric acid in relation to creatinine excretion, biotinylated methylcrotonyl-coenzyme A carboxylase (MCC) and propionyl-coenzyme A

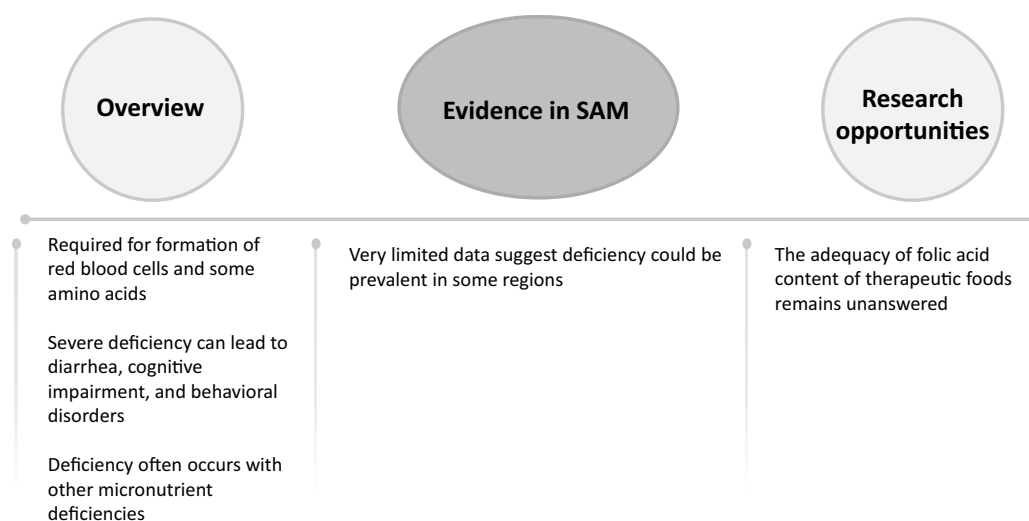


Figure 22 Folic acid take-home messages. Abbreviation: SAM, severe acute malnutrition.

carboxylase (PCC) in lymphocytes.^{31,217} The latter 2 are considered the most reliable indicators because serum and urinary biotin measures do not reflect marginal deficiency.³¹

Two small studies conducted by the same group in Mexico reported evidence of biotin deficiency in children with SAM on admission. In 1 study, plasma biotin concentrations and lymphocyte carboxylase activities (including PCC) were lower in 16 children with SAM compared with a control group. However, urinary biotin concentrations (expressed per gram of creatinine) were higher in children with SAM than in control participants. The authors suggested this may not be indicative of adequate intake of biotin but rather due to increased renal clearance or reduced creatinine excretion, both of which occur with malnutrition.²¹⁸ The same group also noted reduced levels of lymphocyte PCC in 22 patients with SAM, whereas plasma biotin concentrations were not significantly different from those of healthy control participants.²¹⁹ In that study,²¹⁹ patients were randomized to receive either a high-dose biotin supplement (10 mg/d) or placebo for 15 days. Researchers found that children with low lymphocyte PCC levels were the only group to significantly respond to the supplement, confirming their deficiency on admission.²¹⁹

The AI for biotin ranges from 6 to 8 $\mu\text{g}/\text{d}$, depending on age. There is no UL because no adverse effects have been reported, even at a high oral intake of 200 mg/d.³¹ Currently, therapeutic formulas F-75, F-100, and RUTF contain approximately 975%–1381%, 1444%–2062%, and 1470%–2100%, respectively, of the

AI for biotin (Figure 1, see Tables S4–S12 in the Supporting Information online). This translates to daily doses of 65–168 $\mu\text{g}/\text{d}$; it has been recommended that clinical biotin deficiency in children be treated with doses of 5–40 mg/d.²²⁰ Sparse literature suggests that children with SAM may be at risk for biotin deficiency, which may warrant an increase in the amount contained in therapeutic foods. However, there is currently not enough evidence to make conclusive recommendations. See Figure 24 for biotin take-home messages.

DISCUSSION

The introduction of therapeutic foods in the 1990s improved outcomes for children with SAM. However, mortality rates of children under 5 years of age with severe malnutrition continues to be high, especially in children with SAM.^{9,76} Limited studies have investigated the nutritional needs of children with SAM, including caloric requirements,^{221–223} protein requirements,^{224–226} and requirements for some key micronutrients such as vitamin A, vitamin D, thiamine, iron, and selenium. However, overall, little high-quality research has been dedicated to assessing the status of most micronutrients in this population. This review illustrates that concentrations and deficiencies of most micronutrients either have not been previously reported or only reported in a few historical studies of small sample size, and these studies were generally not conducted in an RCT format or in a range of different geographies or subpopulations (eg, sick complicated vs well uncomplicated malnourished children). This is important because the

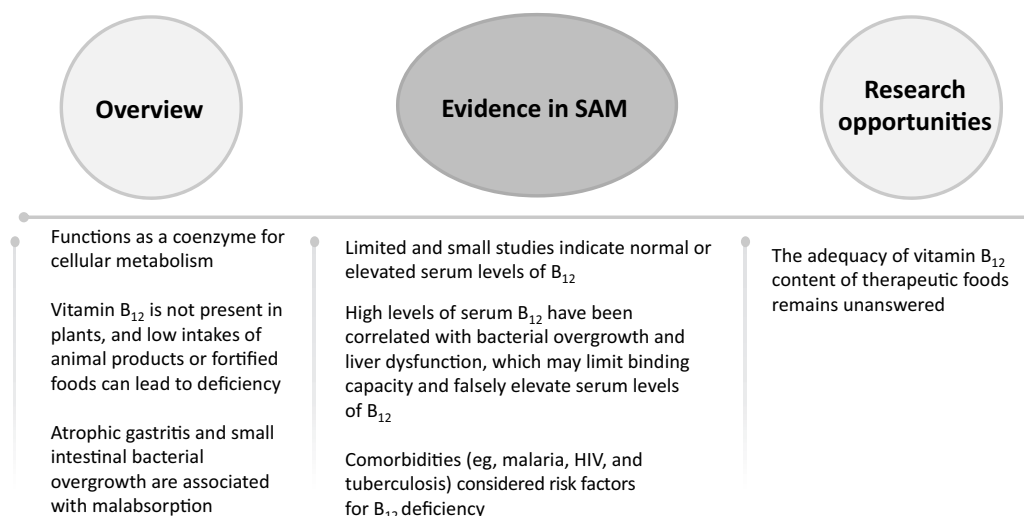


Figure 23 Vitamin B₁₂ take-home messages. Abbreviations: HIV, human immunodeficiency virus; SAM, severe acute malnutrition.

definitions of and treatment protocols for severe malnutrition have changed over time, and research conducted on malnourished children in the 1970s or 1980s may not reflect the current landscape.

Death remains a considerable risk for the children with SAM, even after they finish their treatment of concurrent medical conditions and nutritional rehabilitation,^{11,227} suggesting that other factors may be contributory. A 1-year follow-up study of 1024 children admitted to hospital for treatment of SAM showed that 42% of children died during or after treatment, with 25% of these deaths occurring more than 90 days after admission to hospital.¹¹ A more recent and larger study of 3101 children, including 1218 children with severe malnutrition, reported an overall mortality rate of 20.4%, with 48% of patients died after initial discharge from hospital.⁹ The authors of the same study also reported on factors that were directly or indirectly associated with postdischarge death, including human immunodeficiency virus infection or exposure, underlying medical conditions, and adverse caregiver characteristics.⁹ However, given the intricate role each micronutrient has within the body, as illustrated in Figure 25, the authors believe inadequate micronutrient status may be another important contributory factor to the poor outcomes for children affected with SAM. We believe, therefore, that knowledge of micronutrient status and assessment to ensure adequate micronutrient supplementation in children with SAM should be considered a research priority to guide clinical practice.

In reviewing the literature on micronutrients, there are important relationships with organ dysfunction and

micronutrient status. Although relationships of individual micronutrients to organ systems are discussed in this article, it should also be noted that micronutrients do not work in isolation; often, multiple deficiencies occur at once. From the available evidence, the combination of multiple micronutrient deficiencies is likely to have a significant impact on 1 or more systems (see Figure 25).

Micronutrient status is often different in children with nutritional edema compared with those who present with severe wasting.⁸³ Children with nutritional edema may demonstrate signs of increased oxidative stress, with lower plasma levels of zinc, copper, selenium, and vitamins A and C than those with wasting, yet they tend to have higher levels of free circulating iron, more sodium and potassium pump sites per erythrocyte, and higher fat content in their livers.⁸³ Hence, it is important to explore and compare the micronutrient requirements in patients with nutritional edema and patients with severe wasting.

At the time of their development in the 1990s, F-75 and F-100 were designed for inpatient treatment of both complicated and uncomplicated SAM.¹⁴ In 2007, United Nations agencies endorsed RUTF for the management of uncomplicated SAM in the community.¹⁵ From this point onward, if children did not pass an appetite test or were considered to have medical complications, they were admitted to hospital for treatment with the complicated SAM phenotype. However, the composition of foods used to treat them did not change.

Recently, specifications laid out by the joint WHO and the Food and Agriculture Organization of the United Nations “Codex” group advised on changes to

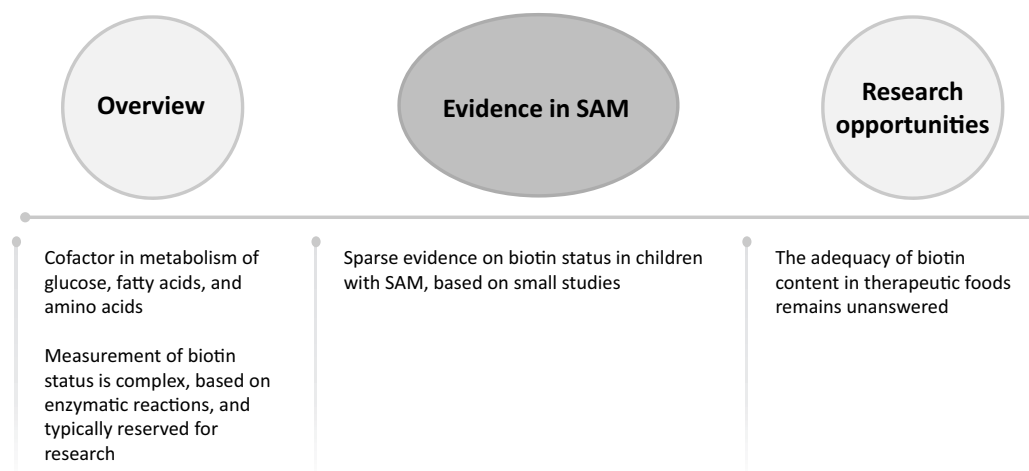


Figure 24 Biotin take-home messages. Abbreviation: SAM, severe acute malnutrition.

the minimum and/or maximum levels of 6 micronutrients included in RUTF (potassium, calcium, phosphorous, magnesium, and vitamins A and D), along with an increase in the essential fatty acid profile.²² The RUTF formulation used for comparison in this narrative review contains micronutrients that already conform to these specified changes.^{18,22}

When assessing micronutrient requirements for children with severe malnutrition, it is difficult to know what constitutes adequacy or deficiency. Although in this review, we used the DRIs as a benchmark to assess micronutrient intake from therapeutic foods, these markers were developed on the basis of the needs of healthy populations and may not reflect the fundamental needs of children with severe malnutrition. It should also be noted that the average weights of children with SAM are in accordance with weights of well infants much younger than those with SAM. This may further limit the use of the DRIs, because the average weights used for their development are based on healthy, typically developing children.²³ In our estimation, based on standard prescriptions of therapeutic foods, most of the micronutrients met or exceeded the AI or RDA for age and some exceeded the UL. The safety of high micronutrient doses, in particular those above the UL, is not well studied in the SAM population and requires close attention. Despite this, biochemical markers for some deficiencies, such as vitamin A and iron, are not always corrected at the end of therapy. This may be a result of saturation of absorption of a micronutrient due to an ongoing need for repletion or higher requirements in the setting of SAM of certain micronutrients.

Nutritional therapy with some micronutrient quantities above the UL may be appropriate for children with SAM and severe micronutrient deficiencies.

Another challenge in assessing micronutrient requirements and, more importantly, in standardized micronutrient quantities in therapeutic foods, is the possible variability of micronutrient status between individual children and between different geographic districts, regions, and countries. Developing therapeutic food micronutrient formulations sufficient to replenish deficiencies or maintain adequate micronutrient levels for most children while ensuring no toxicity and reducing possible adverse effects is a challenging task. Some children or, indeed, populations in certain regions may require additional supplementation to their therapeutic foods. Large-scale studies of micronutrient status at the beginning, during, and end of SAM treatment, which cross multiple contexts or regions as well as children of varying ages, will likely help address this challenge.

It is important to realize when reviewing the available literature that micronutrient status interpretation can be difficult in any population but especially within the severely malnourished population. Multiple biochemical markers for the assessment of the same micronutrient status, different laboratory assays, and varying levels defining micronutrient deficiency complicate the interpretation of results and the comparison of study findings. Additionally, standard biochemical markers of micronutrient status can be affected by different disease states (eg, inflammation).⁹¹ Children with severe malnutrition have systemic inflammation.²²⁸ Systemic inflammation may redistribute micronutrients between

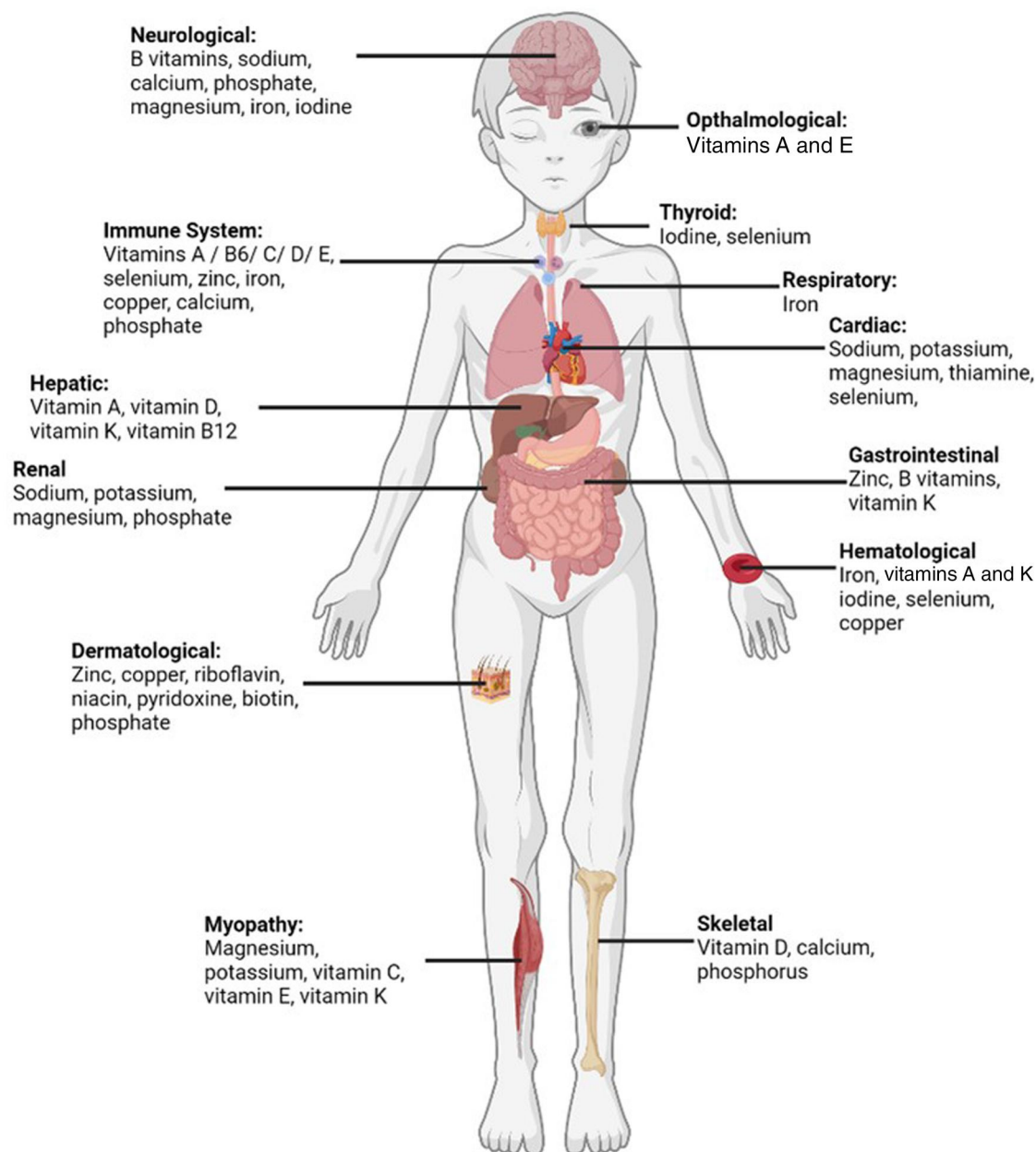


Figure 25 Organ systems affected by altered micronutrient levels. Created with BioRender.com.

tissues and fluid compartments, cause changes in production and loss of carrier proteins, and result in increased excretion of micronutrients or block their use.²²⁹ These processes may skew biochemical markers and affect interpretation of body stores.⁹¹ Although some researchers have adjusted for this inflammation when interpreting biochemical results,²³⁰ it is not always possible, and it remains an important element to consider in addition to recent dietary intake when assessing micronutrient status at admission.

Additionally, it is important that the bioavailability of each micronutrient in therapeutic foods be assessed. Different forms of each micronutrient (eg, heme vs

non-heme iron, varying salt compounds), different forms of therapeutic foods (eg, dairy- and nondairy-based RUTF), disease states commonly seen in severely malnourished children (eg, inflammation, diarrhea, liver dysfunction), and the possibility that the interplay of micronutrients, therapeutic foods, and local diets may all interfere (or enhance, inhibit, or compete) with the bioavailability of each micronutrient.

Future directions

Having knowledge of the micronutrient status at diagnosis, during, and at completion of treatment of SAM is

important, and ensuring adequate micronutrient levels may affect the morbidity and mortality outcomes of children with SAM. Research on micronutrient status at all these points should be considered a priority in children with both complicated and uncomplicated SAM and in children of different age groups to ensure appropriate treatment is provided to address deficiencies. In addition, ideally, region- or context-specific data on micronutrient status will become available, because likely deficiencies of specific micronutrients differ between children with SAM in different regions for reasons related to underlying drivers including availability of different types of foods, infection patterns, rates of premature births and births of small-for-gestational-age babies, maternal nutritional deficits, and so forth. Although, overall, evidence on micronutrient status in children with SAM and subsequent responses to current treatment practices is limited, we recommend prioritizing the areas discussed in the following paragraphs.

Evidence reviewed strongly suggests that the amount of thiamine in therapeutic foods needs urgent attention. As noted earlier, the clinical presentation of children receiving inpatient treatment for SAM has vastly changed since the introduction of therapeutic foods, yet the level of thiamine has not. Given the low risk for toxicity and clear clinical benefit, we think it would be reasonable to increase thiamine supplementation to meet minimal recommendations for refeeding. Specifically, we concur with the suggestion of Hiffler et al¹⁶⁴ that thiamine be increased in F-75 to 7.5 mg/100 mL, which would provide an estimated dose of 50–80 mg/d. Additionally, F-100 and RUTF could be increased to 1 mg/100 mL and 4.5 mg/92 g, respectively, to provide the recommended 1–2 mg/kg/d for children.^{164,166,168}

As noted earlier, IDA remains prevalent among patients upon treatment completion. Promising research has shown improved rates of IDA using higher doses of iron in plant-based versions of RUTF, but the same products resulted in significantly less weight gain than traditional RUTF. It is worth noting that body composition was not commented on in this study, and slower rates of weight gain in the setting of improved body composition may be preferable.²³¹ Regardless, the high prevalence of IDA at completion of treatment makes reviewing iron in therapeutic foods a priority. F-100 does not meet the RDA for iron, and although this product is typically given for a short time, it is important to note that some patients with swallowing dysfunction, such as children with cerebral palsy, rely solely on this product for their rehabilitation. We recommend that the iron content in F-100 be reevaluated and that further studies examining higher iron content in F-100 and RUTF, iron therapy beyond the duration of standard nutritional therapy, or, indeed, other forms

of iron supplementation be conducted to determine the optimal iron dose for children with SAM. These studies must balance the benefits of iron repletion with the potential toxic effects of excess iron in the body, especially in sick infants and children, and the risk of altering the microbiome and stimulating replication of intestinal pathogens.

A recent pilot study has shown that high doses of vitamin D during rehabilitation have promising effects on improving developmental outcomes in children with uncomplicated SAM. With a larger RCT currently underway, it will be important to follow-up these results and consider increasing levels of vitamin D in F-100 and RUTF if this effect persists in this larger study.

CONCLUSION

This review clearly shows there are gaps in research related to micronutrient status and requirements in children with severe wasting and nutritional edema. Moving forward, researchers should prioritize assessment of micronutrient status upon admission, during, and at completion of standard SAM treatment. Specifically, the micronutrients thiamine, iron, and vitamin D should be addressed first. Following this, the effects of either universal changes to supplementation of micronutrients in therapeutic foods or targeted additional individual micronutrient supplementations in specific populations of children with SAM can be assessed in studies. From there, meaningful changes to therapeutic foods can be assessed in studies to help decision-makers formulate policy and ultimately improve clinical practice.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 Micronutrient composition of F-75, F-100, and RUTF

Table S2 Comparison of micronutrient composition of Nutriset formulated RUTF to Codex guidelines 2022

Table S3 Dietary reference intake terms and definitions

Table S4 Predicted intakes of micronutrients from F-75 for children 6-12 months of age weighing 5 kg

Table S5 Predicted intakes of micronutrients from F-75 for children 12-23 months of age weighing 6 kg

Table S6 Predicted intakes of micronutrients from F-75 for children 24-59 months of age weighing 8.5 kg

Table S7 Predicted intakes of micronutrients from F-100 for children 6-12 months of age weighing 5 kg.

Table S8 Predicted intakes of micronutrients from F-100 for children 12-23 months of age weighing 6 kg.

Table S9 Predicted intakes of micronutrients from F-100 for children 24-59 months of age weighing 8.5 kg.

Table S10 Predicted intakes of micronutrients from RUTF for children 6-12 months of age weighing 5 kg.

Table S11 Predicted intakes of micronutrients from RUTF for children 12-23 months of age weighing 6 kg.

Table S12 Predicted intakes of micronutrients from RUTF for children 24-59 months of age weighing 8.5 kg.

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