



Cereals and pulse-based ready-to-use therapeutic food as an alternative to the standard milk- and peanut paste-based formulation for treating severe acute malnutrition: a noninferiority, individually randomized controlled efficacy clinical trial^{1,2}

Paluku Bahwere,^{3,4*} Bisimwa Balaluka,^{5,6} Jonathan CK Wells,⁷ Chobohwa N Mbiribindi,⁵ Kate Sadler,³ Peter Akomo,⁸ Michèle Dramaix-Wilmet,⁴ and Steve Collins³

³Valid International, Oxford, United Kingdom; ⁴Centre for Research in Epidemiology, Biostatistics and Clinical Research, School of Public Health, University of Brussels, Brussels, Belgium; ⁵Lwiro Natural Science Research Centre, South Kivu, Democratic Republic of Congo; ⁶College of Medicine, Catholic University of Bukavu, South Kivu, Democratic Republic of Congo; ⁷Childhood Nutrition Research Centre, University College London Institute of Child Health, London, United Kingdom; and ⁸Valid Nutrition, Cork, Ireland

ABSTRACT

Background: The cost of current standard ready-to-use therapeutic food (RUTF) is among the major obstacles to scaling up community-based management of acute malnutrition (CMAM), an important child survival strategy. Identifying a cheaper alternative is a global public health priority.

Objective: We sought to compare the efficacy of soya-maize-sorghum RUTF (SMS-RUTF) with that of standard peanut paste-based RUTF (P-RUTF).

Design: We used a nonblinded, parallel-group, simple randomized controlled trial along with a day care approach that enrolled 2 groups of children aged 6–23 and 24–59 mo, respectively, with severe acute malnutrition (SAM).

Results: Intention-to-treat (ITT) and per-protocol (PP) analyses showed noninferiority of SMS-RUTF compared with P-RUTF for the recovery rate [ITT: $\Delta = -2.0\%$ (95% CI: -7.6% , 3.6%); PP: -1.9% (95% CI: -5.3% , 1.4%)], weight gain [$\Delta = -0.7 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ (95% CI: -1.3 , $0.0 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$)], and length of stay [$\Delta = 2.0 \text{ d}$ (95% CI: -1.7 , 5.8 d)] in children ≥ 24 mo of age. In children ≤ 23 mo of age, the recovery rate of SMS-RUTF was inferior to that of P-RUTF [ITT: $\Delta = -20.8\%$ (95% CI: -29.9% , -11.7%); PP: -17.2% (95% CI: -25.6% , -8.7%)]. Treatment with SMS-RUTF resulted in a greater increase in hemoglobin [0.670 g/dL (95% CI: 0.420 , 0.921 g/dL); $P < 0.001$]. Treatment with both RUTFs resulted in the replenishment of all of the amino acids tested except for methionine. There were no differences at discharge between RUTF groups in fat mass [$\Delta = 0.3 \text{ kg}$ (95% CI: -0.6 , 1.6 kg); $P = 0.341$] or fat mass index [$\Delta = 0.4 \text{ kg/m}^2$ (95% CI: -0.3 , 1.1 kg/m^2); $P = 0.262$]. By contrast, comparisons of fat-free mass indicated lower concentrations than the community controls after treatment with either of the 2 RUTFs [$\Delta = -1.3 \text{ kg}$ (95% CI: -2.4 , -0.1 kg) and $P = 0.034$ for comparison between community controls and the SMS-RUTF group; $\Delta = -1.8 \text{ kg}$ (95% CI: -2.9 , -0.6 kg) and $P = 0.003$ for comparison between community controls and the P-RUTF group].

Conclusion: SMS-RUTF can be used to treat SAM in children aged ≥ 24 mo to reduce the costs of CMAM programs. More research is required to optimize SMS-RUTF for younger children. This trial

was registered in the Pan African Clinical Trial Registry as PACTR201303000475166. *Am J Clin Nutr* 2016;103:1145–61.

Keywords: severe acute malnutrition, efficacy, ready-to-use therapeutic food, amino acid, bioimpedance analysis, deuterium oxide, hemoglobin, cereals, pulses, milk

INTRODUCTION

Severe acute malnutrition (SAM)⁹ affects approximately 19 million children aged <5 y and is associated with over half a million preventable child deaths each year (1). This figure does not include the edematous form of SAM. Previous figures that included all the forms of SAM have suggested a much higher burden (2). In most developing countries, case fatality rates in hospitals treating SAM remain at 20–30%, and children who require care often cannot access treatment (2). Community-based management of acute malnutrition (CMAM) has been developed to offer a new approach to delivering care to acutely

¹ Supported by the PRANA Foundation and Irish Aid.

² Supplemental Tables 1–6 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at <http://ajcn.nutrition.org>.

*To whom correspondence should be addressed. E-mail: paluku@validinternational.org.

⁹ Abbreviations used: BF, body fat; BIA, bioelectrical impedance analysis; CMAM, community-based management of acute malnutrition; DDT, deuterium dilution technique; DRC, Democratic Republic of Congo; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; HC, health center; IM, illness marker; ITT, intention to treat; LOS, length of stay; MMHZ, Miti-Murhesa Health Zone; MUAC, midupper arm circumference; PA, phytic acid; PhA, phase angle; PP, per protocol; P-RUTF, peanut paste-based ready-to-use therapeutic food; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; SMS-RUTF, soya-maize-sorghum ready-to-use therapeutic food; TBW, total body water.

Received July 21, 2015. Accepted for publication January 26, 2016.

First published online March 16, 2016; doi: 10.3945/ajcn.115.119537.

malnourished children in emergency situations and in more stable settings. The model is rooted in public health principles of coverage and access and is designed to achieve population-wide impact (3). It focuses primarily on treating most acutely malnourished people as outpatients in their homes rather than in therapeutic feeding centers (3). Intensive inpatient care is also provided for those who have complications (3). Techniques of community mobilization are used to engage the affected population and to achieve a high proportion of early presentation while maximizing coverage (3). A study conducted in Malawi on SAM children treated with the use of ready-to-use therapeutic food (RUTF) also demonstrated that most (>85%) of the children discharged as recovered after being treated with the CMAM approach maintained a normal weight-for-height *z* score for as long as 15 mo after discharge (4).

RUTF, a lipid-based and energy-dense paste, resists bacterial contamination, requires no cooking (5), and is a central element of CMAM programs. RUTF production requires grinding all ingredients into a particle size of <200 μm and embedding the protein and carbohydrate components into a lipid matrix (5). The production process avoids introducing water, and the resultant low water activity in the product is critical to RUTF's resistance against bacterial contamination. This in turn allows RUTF to be safely stored at ambient temperatures and used in poor communities (5). The most widely used RUTF, peanut paste-based RUTF (P-RUTF), is a mixture of milk powder, sugar, vegetable oil, peanut butter, vitamins, and minerals (5, 6). It is equivalent to the WHO's F-100 milk (7). This RUTF recipe has been used widely in CMAM to treat severely malnourished children in resource-poor settings (8) with demonstrably high recovery rates and low case fatalities, and a greater weight gain has been demonstrated with the use of P-RUTF (2, 9, 10). However, the high milk content of this formulation makes it very expensive for sustainable use in resource-poor settings and increases the proportion of ingredients that have to be imported into developing countries.

To lower the cost and increase the potential for using locally grown ingredients, Valid Nutrition has developed a new milk- and peanut-free recipe based on locally produced crops. This recipe is made from soya, maize, and sorghum RUTF (SMS-RUTF) and may provide a cheaper alternative to the P-RUTF currently being used. However, the efficacy of this formulation compared with P-RUTF has not been formally demonstrated. An initial study that assessed the effectiveness of SMS-RUTF in Lusaka, Zambia, yielded inconclusive results, with the recovery rates in both the intervention and standard groups below the international Sphere standard and an unexplained high level of mortality (11). Likely explanations of the inconclusive results included the cholera and measles epidemics and floods that occurred during the study period that caused abnormal increases in mortality and default rates (11). Despite these inconclusive results, lessons learned from that trial have been used to improve both the composition of the SMS-RUTF and the design of studies used to evaluate it.

This study examined the efficacy of SMS-RUTF compared with P-RUTF by using a design and context that minimized operational constraints. The SMS-RUTF product that was used had an enhanced phytic acid (PA) and iron and PA and zinc molar ratios and improved the ω -6: ω -3 fatty acid profile ratio (11) compared with the product tested in Lusaka. This study also included a comparison of changes in hemoglobin, amino acid

profile, and body composition during recovery in addition to the standard outcome indicators of recovery rate, weight gain, and length of stay (LOS). The hypotheses assumed were that SMS-RUTF would not be inferior to P-RUTF for the recovery rate, weight gain, and LOS and that treatment with SMS-RUTF would be associated with a higher increase in hemoglobin than would treatment with P-RUTF.

METHODS

Study design

Primary objectives

We used a nonblinded, parallel-group, simple randomized controlled trial (PACTR201303000475166) to compare the efficacy of SMS-RUTF with that on P-RUTF in the treatment of SAM in 2 groups of children—those aged 6–23 mo and those aged 24–59 mo. The noninferiority hypothesis was chosen because the overall aim of the research was to develop a RUTF as effective as the highly effective standard RUTF but cheaper and was assumed based on the result of a previous study into SMS-RUTF we undertook in Lusaka (11). Differences in the color and taste between the SMS- and P-RUTF precluded blinding the study. To ensure that we had full control over all treatment variables and could collect daily data on morbidity, a day care approach was used wherein study subjects attended an outpatient treatment center for 8 h each day to receive standardized treatment protocols. This approach eliminated the risks that subjects shared or sold the RUTF and that the energy and micronutrient densities of the RUTF were altered by inappropriate mixing with other food. It also helped improve the adherence to the study protocol and the accuracy of quantifying individual daily intakes of RUTF.

Secondary objectives

We also compared changes in hemoglobin, the impact on the plasmatic amino acid profile, and changes in body composition attributable to the 2 products. Hemoglobin was measured at both admission and discharge from the study and in a subsample of participants selected randomly throughout the study period. The impact on the plasmatic amino acid profile was assessed by measuring the plasma concentration of the free amino acids (lysine, valine, tryptophan, tyrosine, phenylalanine, methionine, and cysteine) in overnight-fasted malnourished children before starting nutritional rehabilitation, upon discharge from the study, and in age- and sex-matched nonwasted community controls recruited from the same area as the malnourished participants. Body composition was assessed with the use of 2 techniques. **The deuterium dilution technique (DDT) was used to assess total body water (TBW), fat-free mass (FFM), and body fat mass (FM).** This substudy used the change in the concentration of deuterium in samples of saliva after an intake of a standardized oral dose of deuterium oxide to estimate TBW and FM and FFM and derived indexes. It was conducted in a subsample of study subjects at discharge and compared with the concentrations found in age- and sex-matched nonwasted community controls. **Bioelectrical impedance analysis (BIA) was also used to estimate TBW, FM, FFM, and derived indexes. Other specific BIA parameters of reactance and resistance [phase angle (PhA), illness marker] were also measured.** These parameters were assessed with the use of



a dual-frequency portable Bodystat 1500 MDD in another randomly selected subsample of children aged 24–59 mo drawn from each of the treatment groups. These children were assessed at the beginning of nutrition rehabilitation, when their midupper arm circumference (MUAC) reached 12.5 cm, and finally at discharge.

Setting

The study was undertaken in the Miti-Murhesa Health Zone (MMHZ) located in the Kabare administrative zone of South Kivu province in the Democratic Republic of Congo (DRC). The MMHZ covers an area of 525 km² adjacent to Lake Kivu and consists of highland plains and hills at elevations ranging between 900 and 1900 m. It has a tropical highland climate. At the last census in 2011, it had a recorded population of 204,368, with a very high population density of 392 inhabitants per square kilometer. The main economic activities are subsistence agriculture and small-scale trading. In 2011, the MMHZ had 40,000 children aged 6–59 mo, with a prevalence of SAM in these children of 2.2% (12). Breastfeeding is universal, but the prevalence of exclusive breastfeeding until 6 mo is low, with the mean duration being 2.5 mo (13, 14). The diet of infants and young children has remained unchanged for decades and is poor in dairy and other animal source foods (15). The MMHZ has 16 health centers (HCs) and 4 hospitals and before the study started was running a limited CMAM program with 3 outpatient sites for managing SAM without complications and 1 stabilization center for managing SAM with complications. The geographical coverage of this program and the number of admissions were quite low, however (between May and August 2011, only 40 SAM children were admitted into the CMAM program out of a predicted caseload of >800). This study was implemented in 10 of 16 HCs and used 1 hospital as a referral center for stabilizing SAM with complications.

Study populations

The study participants were selected from children admitted into the government-run CMAM program in the MMHZ. The program admitted all children aged 6–59 mo diagnosed with SAM (MUAC <115 mm or bilateral pitting edema of any degree). Length or height was measured, but the related nutrition indexes were not used either in deciding to admit or discharge children or in defining the outcome. Children with an MUAC <115 mm, a good appetite, and no medical complications and those with bilateral pitting edema assessed as + or ++ who also had a good appetite and no medical complications were admitted directly into the day care component of the study program. Those with bilateral pitting edema assessed as +++ or with any medical complications at enrollment were referred to the participating inpatient facility where they received inpatient care until stabilized, after which they were admitted into the day care study program. Children with any medical or nutritional complication during follow-up were also referred to the participating inpatient facility for appropriate treatment of the complication, after which they were readmitted into the day care program and remained in their original study group. Medical complications were defined with the use of the WHO's CMAM and Integrated Management of Childhood Illness standard definitions (2, 16). Inpatient nutritional rehabilitation followed the national guidelines, and therapeutic milks F-75 and F-100 were used as appropriate.

Study subjects were admitted into the study at the same time that they were admitted into the day care phase of the study program. Great attention was given to avoid admitting any children into the study who were not suffering from SAM, and before being included in the study all potential subjects were reexamined by senior supervisors (all of whom had >10 y experience in diagnosing and managing SAM) to confirm that the diagnosis of SAM was correct. The presence of edema, the diagnostic criteria for SAM that is the most difficult to assess, was confirmed by the senior supervisor before enrollment into the study. Children admitted into the CMAM program for whom senior supervisors did not confirm the presence of edema were excluded. Children with congenital or acquired disorders affecting growth, any history of food allergies, a history of being treated for SAM within the previous 3 mo, and those from visiting families were also excluded.

The community control groups for the body composition and amino acid studies were recruited from the same neighborhoods as the malnourished children included in the main study. These controls were matched for the age at enrollment (± 1 mo) and the sex of the malnourished child. Technical difficulties in conducting the BIA assessments in children aged <24 mo meant that only children ≥ 24 –59 mo of age were eligible for inclusion in the BIA component.

Randomization

We used simple randomization (ratio 1:1) for this study. After confirming eligibility for inclusion, children were randomly assigned by a closed-envelope method to receive either SMS-RUTF or P-RUTF. A computer-generated sequentially numbered randomization list (with variable block sizes) that contained both allocations and codes for 900 children was prepared by the trial statistician, who was based outside the DRC. This list was sent to the national study coordinator, who then prepared 900 opaque, sealed, and consecutively numbered randomization envelopes. A block of 20 envelopes was distributed to the enumerator team leaders at each study site and were used to allocate a study group for each subject at admission. The team involved in assessing children for eligibility and in their follow-up had no role in the allocation of the study group.

Monitoring and follow-up

The study was conducted in specially built study day care sites erected at each of the participating HCs. After enrollment, caregivers were asked to bring their children to the nearest site every day between 0800 and 1600 until discharged, and the mother or another family member had to stay with the child. At each site, a minimum of 2 HC nurses and 1 field nutritionist monitored the children's clinical and nutritional parameters, including checking the progress of nutritional recovery and identifying and treating any concurrent infection. At each site, 2 study assistant nurses fed the children with the support of the caregivers. Children were not allowed to take RUTF home, and caregivers were advised not to feed children in the morning before coming to the site—except for children still on breast milk. No special recommendation was given for evening meals. Each study nurse assistant had <10 children to feed. The study nurse assistants were allocated to 1 study group for half of the

study period before being allocated to the other study group for the other half of the study.

Treatment protocol

The nutritional and medical management of children in both study groups was similar and in general followed DRC national guidelines with the exception of the following differences: an admission criteria of MUAC <115 mm or bilateral pitting edema in place of the national criteria of MUAC <110 mm or bilateral pitting edema; a discharge criteria of MUAC $\geq$ 125 mm and no edema for 15 consecutive days in place of the national criteria of MUAC $\geq$ 115 mm and weight gain of 20% and no edema; daily follow-up of children in the study at day care centers instead of weekly at HCs in the national guidelines; and the ad libitum administration of study therapeutic food instead of the fixed amount of 200 kcal $\cdot$ kg⁻¹ $\cdot$ d⁻¹ in the national protocol (17).

After admission into the study, all children received a 5-d course of amoxicillin and a single 500-mg dose of mebendazole. All medications were directly administered to the child by the nurse at the day care sites to ensure that they were taken by the child. Vitamin A was not given because all children had received a high dose of vitamin A of 200,000 IU within 3 mo of admission and because both RUTFs contained a substantial amount of vitamin A (Table 1). For any episodes of infectious disease that occurred during follow-up, any treatment prescribed was also directly administered by the nurses at the day care site.

Data collection and follow-up

We used a combination of specially trained study nurses as supervisors and study assistant nurses and nurses from participating health facilities as enumerators. Two weeks before the start of data collection, all enumerators received training on the diagnosis of SAM, its management, and the follow-up of cases. They were also trained on data collection with the use of an individual monitoring card that had been developed specifically for this study. Data collected on this form included administrative details, nutritional/medical history, physical signs of disease, laboratory results at admission and during nutritional rehabilitation, nutrition variables, clinical signs of diseases, and type of discharge. The nurses collected the data every morning during the period of study participation. A specially designed questionnaire book was used by study assistant nurses to collect additional information, including actual RUTF intake, symptoms, and physical signs of diseases observed during their surveillance of children at the feeding site and symptoms such as bloating, flatulence, abdominal pain, or diarrhea that could have been related to RUTF intake. Special forms were designed and used for collecting specific data for BIA parameters and saliva samples for body composition assessment and blood samples for amino acid assessment. A trial week of the implementation of all protocols and routine data collection procedures preceded the start of the study to ensure the standardization of data collection and to iron out any initial problems.

Procedures

Weight, height, or length and MUAC were measured following procedures recommended by the WHO (18). Hemoglobin concentrations were measured in capillary blood and obtained from

the fingertip with the use of a portable HemoCue hemoglobinometer. The device was calibrated on a daily basis with the use of a HemoCue control cuvette. BIA parameters were determined with the use of the manufacturer-recommended procedures for the hand-foot Bodystat 1500 MDD system (with accompanying measurements of weight and height). BIA was measured with the child in supine position with arms and legs slightly abducted from the trunk. The measurement started after 3–4 min in that position and was performed with the electrodes placed at the dorsal surfaces on the wrist (between the second and third metacarpals) and ankle (between the second and third metatarsals); the proximal and distal electrodes were placed at a minimum of 5 cm apart. The impedance was measured at 50 kHz. The DDT was undertaken in well-hydrated children with empty bladders. Children were considered well hydrated if they had no history of diarrhea during the past week, no history of strenuous activity in the past 3 h, a wet mouth, no history of recent sunken eyes, and no clinically noticeable edema. A single dose of 3 g (children <10 kg) or 6 g (children 10–20 kg) of deuterium was given in the morning after an overnight fast. The deuterium dose was weighed before administration on an electronic scale accurate to 0.01 g. Saliva samples were collected before the deuterium dose (baseline sample), 3 h after ingestion (postdose sample 1), and 4 h after ingestion (postdose sample 2). The children were instructed to refrain from consuming any food or fluid for at least 30 min before the postdose saliva samples. Saliva was collected by getting the children to chew on a ball of cotton wool to fill the ball with saliva. The saliva was then sucked out of the ball by a syringe. A sample collection was deemed successful if at least 2 mL saliva was collected. After collection, saliva samples were stored in a cool box for $\leq$ 6 h before being transferred to a freezer in which they were stored at -20°C until being shipped to the Nairobi-based Kenya Medical Research Institute Laboratory, where they were kept frozen until analysis. The deuterium enrichment in the saliva samples was measured by Fourier transformation infrared spectroscopy (19). In the DDT, TBW was calculated with the use of the value of the deuterium enrichment of the saliva, and the data were analyzed in association with the weight and height measured on the day of dosing. In the BIA analysis, TBW was calculated with the use of a predictive equation developed from anthropometric data and BIA parameters collected in Ethiopian infants and children (20). We deemed this equation to be more appropriate than other published equations. FFM was derived from TBW derived with the use of published age- and sex-specific constants for FFM hydration (21). HIV status was assessed by Determine and Uni-Gold tests with the use of the serial approach as recommended by national guidelines. Plasma samples for amino acid analysis were obtained by venipuncture and collected in tubes with EDTA as an anticoagulant. The blood samples were stored immediately in a cube cooler to maintain blood temperature at 4°C and thereby prevent microhemolysis and the degradation of amino acids by enzymes present in blood cells (22). Samples were transported to a laboratory for centrifugation and deproteinization within 4 h after collection. The blood was centrifuged at $3000 \times g$ for 15 min at 4°C to separate plasma (supernatant) from blood cells. For deproteinization, 100 μL plasma was mixed with 200 μL 5% trichloroacetic acid, and the mixture was centrifuged at $10,000 \times g$ for 10 min at 4°C . The supernatant obtained from this second centrifugation (deproteinized plasma) was then stored at -20°C



TABLE 1
Ingredients and nutrients of the study foods¹

	SMS-RUTF	P-RUTF	UN specifications ²
Ingredients, g/100 g			
Soybean, dehulled	38.6	0.0	
Maize, degerminated	4.0	0.0	
Sorghum: white, whole grain	10.0	0.0	
Dried skim milk	0.0	25.0	
Sugar	16.7	27.4	
Peanut paste	0.0	26.0	
Palm oil	21.6	20.0	
Linseed oil	2.1	0.0	
Palm stearin	4.0	0.0	
Vitamin and minerals premix	3.0	1.6	
Nutrients			
Energy, kcal/100 g	553	530	520–550
Protein:energy ratio, %	11.9	12	10–12
Fat:energy ratio, %	59.1	56.0	45–60
ω -6:Energy ratio, %	12.3		3–10
ω -3:Energy ratio, %	3.1		0.3–2.5
ω -6: ω -3 Ratio, %	4.0		5–9
Vitamin A, μ g/100 g	1000	910	810–1100
Vitamin C, mg/100 g	329	53	$\geq$ 50
Vitamin D, μ g/100 g	14	16	15–20
Vitamin E, mg/100 g	40.7	20	$\geq$ 20
Thiamin (vitamin B-1), mg/100 g	1.4	0.6	$\geq$ 0.5
Riboflavin (vitamin B-2), mg/100 g	1.9	1.8	$\geq$ 1.6
Niacin (vitamin B-3), mg/100 g	19	5.3	$\geq$ 5
Pantothenic acid (vitamin B-5), mg/100 g	8.3	3.1	$\geq$ 3
Pyridoxine (vitamin B-6), mg/100 g	1.4	0.6	$\geq$ 0.6
Biotin (vitamin B-7), μ g/100 g	56	65	$\geq$ 60
Folates (vitamin B-9), μ g/100 g	370	210	$\geq$ 200
Cobalamin (vitamin B-12), μ g/100 g	4.3	1.8	$\geq$ 1.6
Vitamin K, μ g/100 g	14	21	15–30
Calcium, mg/100 g	437.8	315	300–600
Phosphorus, mg/100 g	446.0	370	300–600
Magnesium, mg/100 g	74	86	60–140
Potassium, mg/100 g	1155.8	1140	1100–1400
Copper, mg/100 g	0.9	1.7	1.4–1.8
Iodine, μ g/100 g	417	100	70–140
Iron, mg/100 g	43.8	12	10–14
Zinc, mg/100 g	18.5	11.1	11–14
Antinutrients			
Phytic acid, mg/100 g	420	255	<100
Phytic acid:zinc ratio, %	2.0	2.2	<15
Phytic acid:iron ratio, %	0.8	1.9	<1

¹P-RUTF, peanut paste-based ready-to-use therapeutic food; SMS-RUTF, soya-maize-sorghum ready-to-use therapeutic food.²Obtained from references 4, 15, and 16.

until it was shipped in bulk to the Ajinomoto laboratory in Japan, where the amino acid was measured by a Hitachi High-Technologies L-8900 dedicated automated amino acid analyzer composed of a guard and analytic column following standard instruction from the device manufacturer (23).

Food products used in the study

Both study RUTFs were produced in the Valid Nutrition factory in Malawi, an officially recognized UNICEF RUTF supplier. The factory has been supplying the Ministry of Health in Malawi since 2005 and has produced study foods for several published studies (11, 24–30). Table 1 provides the composition of the 2 RUTFs obtained from the USDA food composition

database, and **Table 2** compares their amino acid profiles obtained from actual laboratory analysis of the 2 products. The 2 types of RUTFs were packed in similar sachets with different-colored labels. On the basis of our experiences from the Lusaka trial, we modified the micronutrient profile of the SMS-RUTF product used in this study. We used specially formulated vitamin and mineral premixes and dehulled soybean and degerminated maize. The final product met the WHO 2007 recommendations for RUTF mineral and vitamin levels. To compensate for the higher PA content in the SMS-RUTF and improve the PA:iron and PA:zinc molar ratios, we increased the concentration of iron and zinc in the SMS-RUTF above the WHO-recommended concentrations (31, 32). To improve iron bioavailability in the SMS-RUTF, we increased the vitamin C content above the



TABLE 2Comparison of the amino acid profile of the study RUTFs obtained by laboratory analysis¹

Amino acid	SMS-RUTF, g/100 g	P-RUTF, g/100 g	SMS-RUTF:P-RUTF ratio	Adjusted SMS-RUTF:P-RUTF ratio ²
Cystine	0.31	0.18	1.72	1.54
Methionine	0.22	0.25	0.88	0.78
Aspartic acid	1.95	1.39	1.40	1.24
Threonine	0.70	0.54	1.30	1.16
Serine	0.94	0.82	1.15	1.02
Glutamic acid	3.24	3.01	1.08	0.96
Glycine	0.74	0.53	1.40	1.25
Alanine	0.81	0.52	1.56	1.37
Valine	0.77	0.71	1.08	0.96
Isoleucine	0.77	0.60	1.28	1.14
Leucine	1.41	1.20	1.12	1.03
Tyrosine	0.51	0.56	0.91	0.81
Phenylalanine	0.86	0.72	1.19	1.06
Lysine	1.05	0.93	1.30	1.01
Histidine	0.46	0.37	1.24	1.11
Arginine	1.21	1.01	1.20	1.08
Proline	0.94	1.07	0.88	0.79
Tryptophan	0.24	0.20	1.20	1.07

¹P-RUTF, peanut paste-based ready-to-use therapeutic food; RUTF, ready-to-use therapeutic food; SMS-RUTF, soya-maize-sorghum ready-to-use therapeutic food.

²Adjusted with the use of the true protein digestibility for soybean, sorghum, and corn flour for the SMS-RUTF and milk and peanut butter for the P-RUTF.

WHO recommendations. We also increased the n-3 PUFA content and decreased the n-6 PUFA content to obtain an n-6 PUFA:n-3 PUFA ratio <5 (33).

A pretrial panel test demonstrated that the previously discussed changes did not affect consistency, color, odor, or taste compared with the product used in the Lusaka trial; therefore, we did not repeat acceptability trials on the product. However, to ascertain and compare the acceptability of the 2 trial products in particular regard to the difference in iron, lactose, and nondigestible oligosaccharide content, we collected data during the efficacy trial on abdominal pain, the occurrence of diarrhea, flatulence, abdominal distension, and actual daily intake (34, 35).

Outcomes

The primary outcomes of interest for this study were recovery rate, mean daily weight gain, and mean LOS. Secondary outcomes included hemoglobin change and differences in FM, body fat (BF) percentage and fat mass index, FFM, and fat-free mass index (FFMI), PhA, and illness marker (IM). The plasma concentrations of 8 key amino acids at discharge were also studied.

Sample size

We calculated the sample size to demonstrate that SMS-RUTF was not inferior to P-RUTF for the recovery rate, weight gain, and LOS among children with SAM discharged as recovered from the study. The sample sizes were calculated for a power of 80% and a level of statistical significance of 0.05. The margins of non-inferiority were 10% for recovery rate, $1.2 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ for weight gain, and 14 d for LOS. These margins were defined based on the findings of our previous study conducted in Lusaka (11). For the recovery rate, the margin of noninferiority of 10% was fixed based on the Lusaka SMS-RUTF study that suggested a re-

covery rate of >80% for the standard treatment [per-protocol (PP) analysis] and the Sphere standard requirement of a minimum recovery of 75%. Based on data from the SMS-RUTF Lusaka study in which the weight gain rate for the P-RUTF was $3.3 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ (95% CI: $2.8, 3.7 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$), the margin of noninferiority was fixed at $1.2 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. The 14-d non-inferiority margin for LOS was fixed based on the cost of the program and the fact that common practice is to follow-up these children either weekly or once every 2 wk. We estimated that a difference of 14 d would be associated with a considerable increase in the cost of treatment in a context of a restricted budget. Because the findings of our previous study in Lusaka indicated potentially different responses between younger and older children, sample sizes were calculated separately for children aged 6–23 mo and for those aged 24–59 mo (11). The sample size was calculated with the use of the Internet-based software Power (36). A total of 448 SAM children aged 6–23 mo and 316 SAM children aged 24–59 mo were required to be 80% sure that the lower limit of a 1-sided 95% CI would be above the set limits of noninferiority (37, 38). Because of budgetary constraints, the following convenience samples were chosen for the secondary objectives: 200 SAM children (100/study group) for hemoglobin; 60 SAM children (30/study group) and 60 age- and sex-matched community controls for body composition with the use of the DDT; 200 SAM children (100/study group) for body composition with the use of BIA; and 60 SAM children and 25 age- and sex-matched controls for determining the distribution of free amino acid concentrations.

Data management, definitions, and analysis

Data management

Throughout the study, the data quality manager and principal investigator conducted field supervisions during which they spot-checked the quality of anthropometric measurements,



edema diagnosis, individual data collection forms, and the content of the study questionnaires. All individual data collection forms were checked again for accuracy and completeness at discharge. The verified forms were then collected for data entry. Data were double-entered by 2 enumerators into a customized EpiData database prepared for this study (39). Data entry quality was monitored by the supervisors, who cross-checked a random selection of 10% of the records. Given that independent teams regularly verified anthropometric measurements, no value was excluded. Cleaned data were exported to Stata version 12 (40) for analysis.

Definitions

Recovery rates were defined as the percentage of children who were discharged as recovered from the study divided by the total number of children who exited the study. The total of children who exited the study included all those who defaulted, died, or were discharged as nonrecovered either after meeting the nonrecovered criteria (90 d in the program) or at the closure of the program. A child was considered to have defaulted if he or she was absent for 5 consecutive daily visits or refused to return after 2 community worker home visits.

Rates of weight gain were calculated by dividing the weight gain expressed in g (weight at exit – weight at admission) by the weight at admission (in kg) and LOS (in d). Mean weight gains were measured as the mean of the individual weight gains and expressed as $\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. The mean LOS was calculated by dividing the sum of individual LOSs by the total number of children included in the numerator calculation. The hemoglobin change was the difference in blood hemoglobin concentrations between admission and discharge from the study in all children, with measurements taken at both points.

FM in both the DDT and BIA was calculated as the difference between body weight and FFM. Percentage BF was obtained by the equation $\%BF = (FM \times 100)/\text{body weight}$. The FFMI (FFM divided by the square of the height) and fat mass index (fat mass divided by the square of the height) were obtained by dividing FFM and FM expressed in kg by the square of the height expressed in m. **Resistance and reactance were adjusted for height by dividing the observed values of these BIA parameters by the height of the child (41). PhA and IM were calculated directly by the BIA Bodystat 1500 MDD.**

Analysis

Means and SDs, medians, IQRs (proportions), and 95% CIs were used to describe the admission and exit parameters as appropriate. Means were compared with the use of a *t* test, medians with the use of the Mantel-Haenszel test, and proportions with the use of Student's chi-square test. Differences in the estimated marginal mean between the treatment groups along with a bootstrapped 95% CI were estimated to infer noninferiority.

For the primary outcomes, in accordance with recommendations for analyzing and reporting equivalence and noninferiority studies, both intention-to-treat (ITT) and PP analyses were performed, and the 95% CIs were used to interpret any differences (42, 43). The ITT analyses included all children enrolled in the study. The PP analyses for recovery rates included all children discharged out of the program as recovered, dead, or nonrecovered but excluded children who defaulted or who transferred out of the program and were lost to follow-up after inpatient

transfer. The PP analyses for weight gains included only the children who were discharged as recovered. Logistic regression was used to test for interactions between the recovery rate and other variables. For the secondary outcomes, means were compared with the use of Student's 2-tailed *t* test, and medians were compared with the use of the Kruskal-Wallis test. Bonferroni correction was applied in case of multiple comparisons of means or medians, and the *P* value at which statistical significance was reached was adjusted accordingly. Multiple linear regression was used to model the effect of SMS-RUTF on hemoglobin increase.

Ethical considerations

Permission to conduct the study was obtained from the Ethics Committee of the Catholic University of Bukavu. At the time of admission, each child's parent or caregiver was informed about the nature and purpose of the study and was asked for verbal and written consent for his or her child to be included and for the medical information to be used for research purposes. When parents or caregivers withheld consent for participation, children were referred to 1 of the 4 nonparticipating clinics providing care for SAM in the MMHZ. These clinics were supported by the DRC and UNICEF. They used standard P-RUTF procured from France. The other benefit of participating included free medical care for any episode of disease during the follow-up and 1 porridge meal/d given to caregivers when looking after their children at the feeding site.

A data safety monitoring board was assigned to perform an ongoing review of study outcomes based on the data they extracted from either the study subject's files or the study database during the bimonthly visit. The findings served only to decide whether the study should be ended because of an indication of serious side effects. No serious side effects were detected, and no reasons for interrupting the study were identified.

RESULTS

Enrollment and movement of subjects from preliminary screening to data analysis for the whole cohort and by age are shown in **Figure 1**. Between March 2013 and February 2014, a total of 924 eligible children were screened; 886 of them were randomly assigned to either the SMS-RUTF (*n* = 445) or the P-RUTF (*n* = 441) study group. Thirty-eight eligible children were excluded before being randomly assigned, and another 11 children (6 in the SMS-RUTF group and 5 in the P-RUTF group) withdrew from the study after only 1 d of attendance because they could not fulfill the daily attendance requirement. This was classified as "after first day refusal."

Baseline characteristics of children included in the ITT analyses for each study group are shown in **Table 3**. Marasmus was the dominant form of SAM among children enrolled in the study, and there was no significant difference between groups at baseline for the variables considered in either of the 2 age categories.

Program outcomes: recovery, mortality, defaulter, and nonresponse

In children aged 24–59 mo, the results of the ITT analysis showed that both products met minimum international standards. In the SMS-RUTF group, recovery, mortality, defaulter, and nonresponse rates were 88.3% (204/231), 1.7% (4/231), 7.8% (18/231), and 2.2% (5/231), respectively. In the P-RUTF

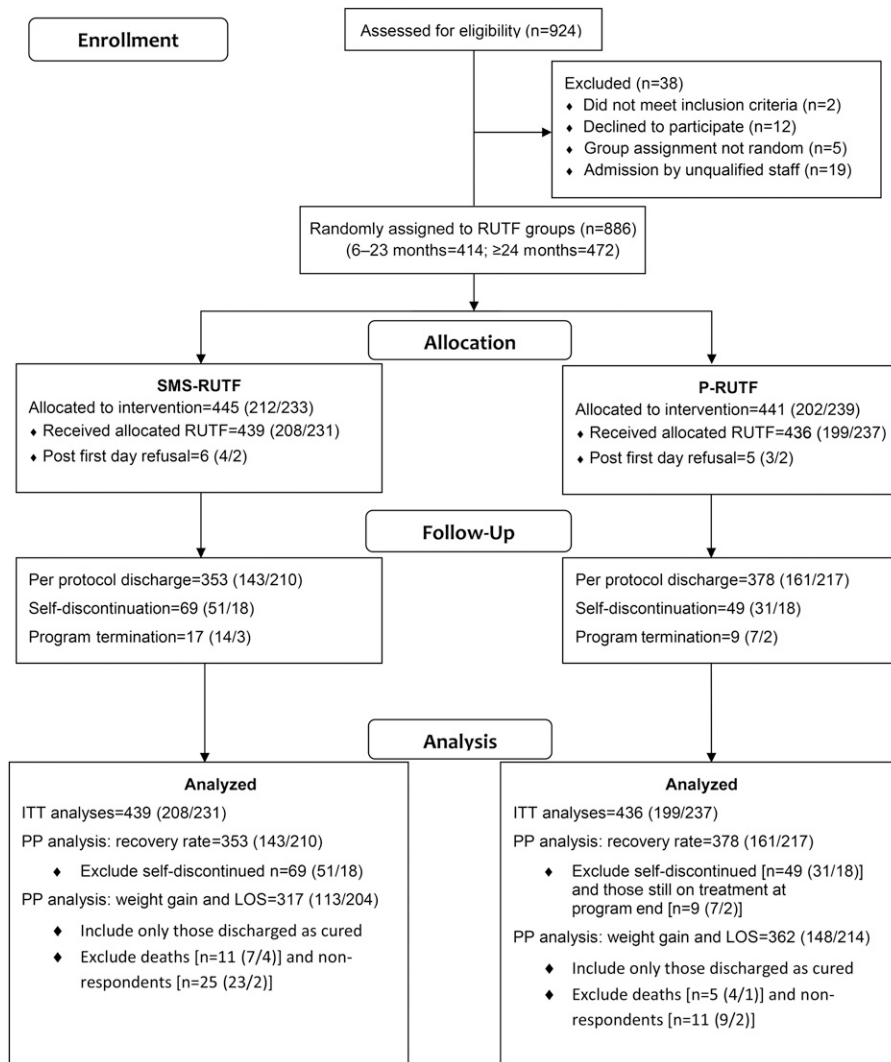


FIGURE 1 Study participants flow diagram. ITT, intention to treat; LOS, length of stay; PP, per protocol; P-RUTF, peanut paste-based ready-to-use therapeutic food; RUTF, ready-to-use therapeutic food; SMS-RUTF, soya-maize-sorghum ready-to-use therapeutic food.

group, the results were 90.3% (214/237), 0.4% (1/237), 7.6% (18/237), and 1.7% (4/237), respectively.

By contrast, in children aged 6–23 mo, the ITT analysis demonstrated that minimum international standards were met for the P-RUTF group but not for the SMS-RUTF group. In this age category, the SMS-RUTF group's recovery, mortality, defaulter, and nonresponse rates were 54.3% (113/208), 3.4% (7/208), 24.5% (51/208), and 17.8% (37/208), respectively, compared with 75.1% (148/197), 1.0% (2/197), 15.7% (31/197), and 8.1% (16/197), respectively, in the P-RUTF group.

Primary outcomes

Both ITT and PP analyses showed that in children aged 24–59 mo, the recovery rate (predefined noninferiority margin of $\Delta = 10\%$) of the SMS-RUTF group was not inferior to the recovery rate of the P-RUTF group [ITT: $\Delta = -2.0\%$ (95% CI: -7.6% , 3.6%); PP: -1.9% (95% CI: -5.3% , 1.4%)]. By contrast, in children aged 6–23 mo, the recovery rate in the SMS-RUTF group was inferior to that in the P-RUTF group [ITT: $\Delta = -20.8\%$ (95% CI: -29.9% , -11.7%); PP: -17.2% (95% CI: -25.6% , -8.7%)] (**Figures 2**

and **3**). The PP analysis for weight gain in children who were discharged as recovered showed that the SMS-RUTF group was not inferior to the P-RUTF group (predefined noninferiority margin of $\Delta = 1.2 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) either in children aged 24–59 mo [$\Delta = -0.7 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ (95% CI: -1.3 , $0.0 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$)] or in those aged 6–23 mo [$\Delta = -0.6 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ (95% CI: -1.5 , $0.3 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$)] (**Figure 4**). SMS-RUTF was not inferior to P-RUTF in terms of LOS (predefined noninferiority margin of $\Delta = 14 \text{ d}$) both in the ITT analysis [$\Delta = +2.0 \text{ d}$ (95% CI: -1.7 , 5.8 d) in children aged 24–59 mo and $+2.4 \text{ d}$ (95% CI: -3.2 , 8.1 d) in those aged 6–23 mo] and among recovered children [$\Delta = +2.4 \text{ d}$ (95% CI: -1.2 , 6.0 d) in children aged 24–59 mo and $+3.9 \text{ d}$ (95% CI: -1.8 , 9.6 d) in those aged 6–23 mo] (**Figure 5**).

Results of the secondary outcomes

Hemoglobin

The unadjusted analysis showed no difference in the mean hemoglobin changes between the 2 RUTF groups for all children evaluated [$+1.04 \text{ g/dL}$ (95% CI: 0.79 , 1.30 g/dL) for SMS-RUTF compared with $+1.06 \text{ g/dL}$ (95% CI: 0.84 , 1.28 g/dL),

TABLE 3Baseline characteristics for children included in the intention-to-treat analysis¹

Criteria	6–23 mo		24–59 mo	
	SMS-RUTF	P-RUTF	SMS-RUTF	P-RUTF
<i>n</i>	208	199	231	237
Sociodemographic characteristics				
Male, <i>n</i> (%)	110 (52.9)	93 (46.7)	115 (49.8)	108 (45.6)
Age, mo	15.8 ± 5.3	15.3 ± 5.5	42.4 ± 11.4	44.2 ± 12.1
Mother alive, <i>n</i> (%)	203 (97.6)	190 (95.5)	223 (96.5)	229 (96.6)
Father alive, <i>n</i> (%)	200 (96.1)	190 (95.5)	221 (95.7)	227 (95.8)
Mother's main income from farming own land, <i>n</i> (%)	153 (73.6)	150 (75.4)	159 (68.8)	171 (72.1)
Nutrition characteristics (all)				
Midupper arm circumference, cm	10.9 ± 0.8	10.9 ± 1.0	11.5 ± 1.0	11.3 ± 0.9
Weight, kg	6.2 ± 1.1	6.3 ± 1.2	8.8 ± 1.6	8.6 ± 1.6
Length/height, cm	67.2 ± 5.0	67.2 ± 5.2	80.2 ± 7.8	80.1 ± 7.5
Bilateral pitting edema, <i>n</i> (%)	28 (13.5)	27 (13.6)	69 (29.9)	57 (24.0)
Weight-for-age <i>z</i> score	−4.0 ± 1.0	−3.9 ± 1.2	−4.2 ± 1.0	−4.4 ± 0.9
Height-for-age <i>z</i> score	−4.3 ± 1.5	−4.0 ± 1.6	−4.8 ± 1.4	−5.0 ± 1.4
Weight-for-height <i>z</i> score	−2.4 ± 1.1	−2.4 ± 1.2	−2.2 ± 1.3	−2.4 ± 1.3
Nutrition characteristics (children without edema), <i>n</i>				
Midupper arm circumference, cm	10.8 ± 0.6	10.8 ± 0.8	11.1 ± 0.5	11.1 ± 0.4
Weight, kg	6.1 ± 1.0	6.1 ± 1.1	8.5 ± 1.4	8.5 ± 1.3
Length/height, cm	66.7 ± 4.7	66.6 ± 5.0	79.9 ± 7.9	79.9 ± 7.7
Weight-for-age <i>z</i> score	−4.1 ± 1.0	−4.0 ± 1.1	−4.4 ± 0.8	−4.5 ± 0.9
Height-for-age <i>z</i> score	−4.3 ± 1.5	−4.1 ± 1.7	−4.9 ± 1.5	−5.0 ± 1.4
Weight-for-height <i>z</i> score	−2.5 ± 1.1	−2.5 ± 1.1	−2.5 ± 1.1	−2.6 ± 1.1
Nutrition characteristics (children with edema), <i>n</i>				
Midupper arm circumference, cm	11.6 ± 1.5	11.9 ± 1.5	12.3 ± 1.2	12.0 ± 1.5
Weight, kg	7.2 ± 1.4	7.5 ± 1.4	9.6 ± 1.9	9.2 ± 2.0
Length/height, cm	70.5 ± 5.9	71.1 ± 4.3	81.1 ± 7.3	80.9 ± 6.7
Weight-for-age <i>z</i> score	−3.4 ± 1.2	−3.2 ± 1.3	−3.6 ± 1.1	−4.1 ± 1.1
Height-for-age <i>z</i> score	−3.9 ± 1.7	−3.7 ± 1.4	−4.6 ± 1.3	−4.9 ± 1.2
Weight-for-height <i>z</i> score	−1.9 ± 1.3	−1.7 ± 1.6	−1.5 ± 1.1	−1.9 ± 1.1

¹All values are means ± SDs unless otherwise indicated. P-RUTF, peanut paste-based ready-to-use therapeutic food; SMS-RUTF, soya-maize-sorghum ready-to-use therapeutic food.

a difference of 0.02 g/dL (95% CI: −0.31, 0.35 g/dL; $P = 0.921$) and for those discharged as recovered [+1.23 g/dL (95% CI: 0.95, 1.50 g/dL) for SMS-RUTF compared with +1.19 g/dL (95% CI: 0.90, 1.47 g/dL), a difference of 0.04 g/dL (95% CI: −0.35, 0.44 g/dL; $P = 0.837$]. The difference in the proportion of anemic children (hemoglobin <11.0 g/dL) in children discharged as recovered was also not statistically significant [26.39% (19/72) for SMS-RUTF and 30% (24/80) for P-RUTF, a difference of −3.61% (95% CI: −17.91%, 10.69%); $P = 0.622$]. The study was underpowered to reach a level of statistical significance for the differences observed. A linear regression analysis adjusting for age, sex, hemoglobin at admission, daily energy intake from RUTF, study LOS, and growth velocity (see **Supplemental Table 1** for full results of the linear regression) indicated that treatment with SMS-RUTF was associated with a statistically significant increase in hemoglobin of 0.670 g/dL (95% CI: 0.420, 0.921 g/dL) compared with children treated with P-RUTF ($P < 0.001$). The difference of 0.743 g/dL (95% CI: 0.427, 1.059 g/dL) when only children discharged as recovered were included in the analysis was also significant ($P < 0.001$).

Amino acids

The overnight-fasting plasma concentrations of the tested free amino acids did not differ according to the RUTF group at ad-

mission. A comparison of mean plasma concentrations of malnourished children and the mean concentrations of the community control children without acute malnutrition

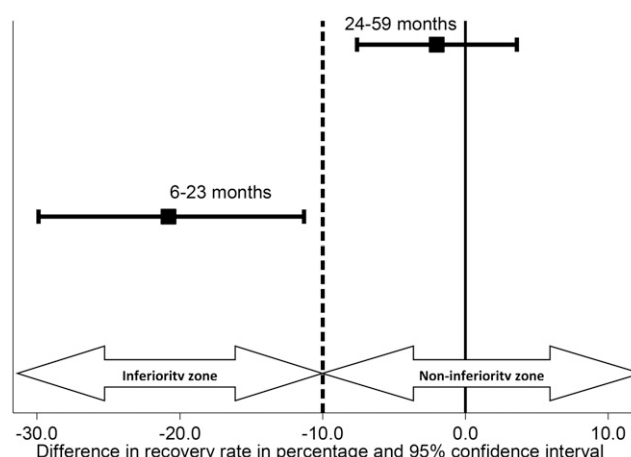


FIGURE 2 Intention-to-treat analysis: difference in recovery rate between the SMS-RUTF [$n = 439$ (208/231)] and P-RUTF [$n = 436$ (199/237)] for both age groups. The difference in estimated marginal means and their bootstrapped 95% CIs were compared; n indicates the total n for the RUTF group, the n for children aged 6–23 mo, and the n for children aged 24–59 mo. P-RUTF, peanut paste-based ready-to-use therapeutic food; RUTF, ready-to-use therapeutic food; SMS-RUTF, soya-maize-sorghum ready-to-use therapeutic food.

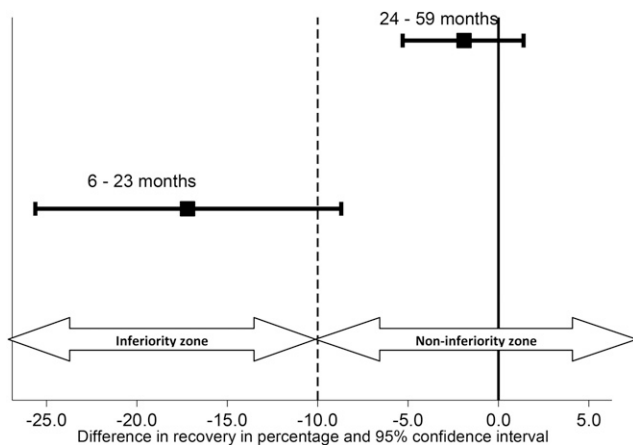


FIGURE 3 Per-protocol analysis: difference in recovery rate between the SMS-RUTF [$n = 353$ (143/210)] and P-RUTF [$n = 378$ (161/217)] for both age groups. The difference in estimated marginal means and their bootstrapped 95% CIs were compared; n indicates the total n for the RUTF group, the n for children aged 6–23 mo, and the n for children aged 24–59 mo. P-RUTF, peanut paste-based ready-to-use therapeutic food; RUTF, ready-to-use therapeutic food; SMS-RUTF, soya-maize-sorghum ready-to-use therapeutic food.

showed that malnourished children enrolled in both groups had a significantly reduced concentration of several of these amino acids (Table 4). Nutritional rehabilitation with both SMS-RUTF and P-RUTF resulted in the replenishment of all of the amino acids tested by the time of discharge except for methionine (Table 4). Stratified analyses showed that in children aged 6–23 mo, the deficit was corrected at the time of discharge for all of the tested amino acids, whereas in older children, plasma concentrations of both methionine and phenylalanine remained lower than the community controls at the time of discharge (Supplemental Tables 2 and 3).

Body composition

For children discharged as recovered, there were no differences at discharge between RUTF groups or between the RUTF groups and the community controls in FM or fat mass index in the DDT substudy (Table 5). By contrast, pairwise comparisons of FFM indicated that children after treatment with either of the 2 RUTFs had significantly lower concentrations of FFM than the community controls (Table 5), but this difference disappeared after adjusting for height.

The comparison of the BIA parameters between the subsamples of SAM children tested at admission and again at the time of reaching an MUAC of 125 mm showed no significant differences between children in the 2 intervention groups (Supplemental Table 4). However, at discharge, children in the SMS-RUTF group had a higher IM and lower FFMI, PhA, and reactance:height ratio compared with children in the P-RUTF group (Table 6). The SMS-RUTF BIA subgroup also tended to have a greater height than the P-RUTF BIA subgroup. Technical challenges (lack of cooperation from children at the beginning of the nutritional rehabilitation or the presence of edema) limited the number of children with a successful BIA measurement at admission (43 surveyed out of the 200 selected) and at the time of reaching an MUAC of 12.5 cm (57 children surveyed out of 200 selected), reducing the statistical power of the BIA

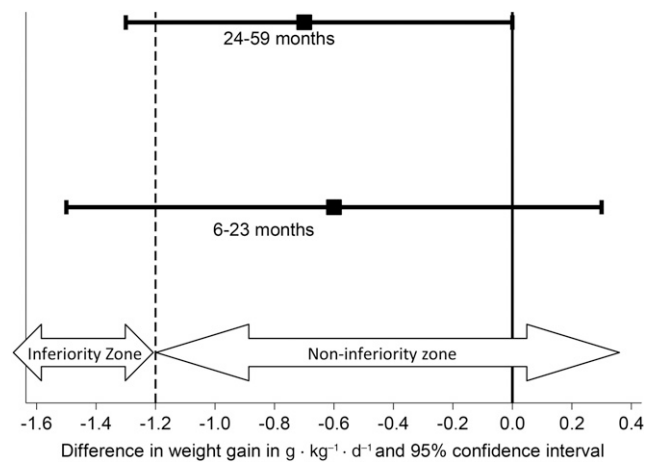


FIGURE 4 Per-protocol analysis: difference in daily weight gain between the SMS-RUTF [$n = 317$ (113/204)] and P-RUTF [$n = 362$ (148/214)] for both age groups. The difference in estimated marginal means and their bootstrapped 95% CIs were compared; n indicates the total n for the RUTF group, the n for children aged 6–23 mo, and the n for children aged 24–59 mo. P-RUTF, peanut paste-based ready-to-use therapeutic food; RUTF, ready-to-use therapeutic food; SMS-RUTF, soya-maize-sorghum ready-to-use therapeutic food.

analysis at these time points. At discharge, the number of children surveyed was 164 children out of the 200 selected.

Linear growth

Overall, there was no clinically relevant catch up in height for age during treatment and no significant differences in linear growth between the RUTF groups. The severity of stunting in children aged 6–23 mo at enrollment increased very slightly over the study period, whereas in children aged 24–59 mo there was a small but clinically insignificant improvement. Within-group analysis showed that the daily incremental length gains were not different between children discharged as recovered and children discharged as nonrecovered (Supplemental Table 5).

RUTF intake, acceptability, and tolerance

RUTF intake

The intake of RUTF was higher for children in the P-RUTF group. For children aged 6–23 mo, the mean $\pm$ SD daily intake was 183.2 ± 76.3 g/d for SMS-RUTF compared with 207.8 ± 76.4 g/d for P-RUTF, a mean difference of -24.6 g/d (95% CI: $-39.6, -9.6$ g/d; $P = 0.001$). For children aged 24–59 mo, the mean $\pm$ SD daily intake was 243.8 ± 86.8 g/d for SMS-RUTF compared with 272.7 ± 77.9 g/d for P-RUTF, a mean difference of -28.9 g/d (95% CI: $-43.94, -13.9$ g/d; $P < 0.001$) (Supplemental Table 6).

Energy intake was significantly higher in children aged 24–59 mo receiving P-RUTF than in the same age group receiving SMS-RUTF [142.7 ± 50.8 kcal $\cdot$ kg $^{-1}$ $\cdot$ d $^{-1}$ for SMS-RUTF compared with 157.2 ± 51.9 kcal $\cdot$ kg $^{-1}$ $\cdot$ d $^{-1}$ in the P-RUTF group, a mean difference of -18.63 (95% CI: $-27.65, -9.51$ kcal $\cdot$ kg $^{-1}$ $\cdot$ d $^{-1}$; $P < 0.001$). The differences in energy intakes in the younger age group [149.5 ± 82.9 kcal $\cdot$ kg $^{-1}$ $\cdot$ d $^{-1}$ for SMS-RUTF compared with 165.7 ± 58.7 for P-RUTF, a mean difference of -16.2 kcal $\cdot$ kg $^{-1}$ $\cdot$ d $^{-1}$ (95% CI: $-30.4, -2.0$ kcal $\cdot$ kg $^{-1}$ $\cdot$ d $^{-1}$)] were also significant ($P = 0.026$). Within

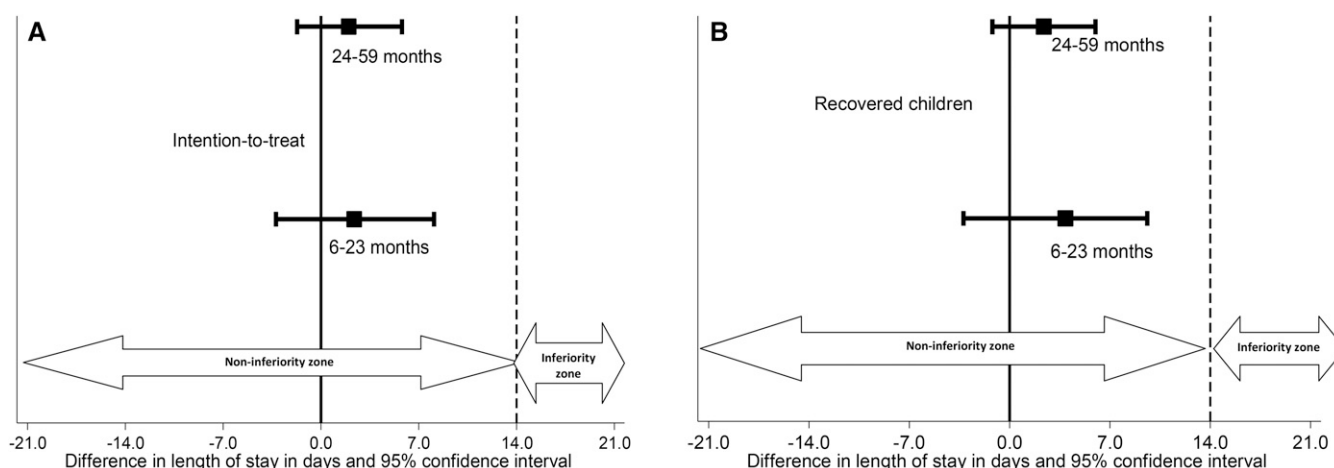


FIGURE 5 Difference in the length of stay between the SMS-RUTF [$n = 439$ (208/231)] and P-RUTF [$n = 436$ (199/237)] for both age groups in the intention-to-treat analysis (A) and between recovered children (B) of the SMS-RUTF [$n = 317$ (113/204)] and P-RUTF [$n = 362$ (148/214)]. The difference in estimated marginal means and their bootstrapped 95% CIs were compared; n indicates the total n for the RUTF group, the n for children aged 6–23 mo, and the n for children aged 24–59 mo. P-RUTF, peanut paste-based ready-to-use therapeutic food; RUTF, ready-to-use therapeutic food; SMS-RUTF, soya-maize-sorghum ready-to-use therapeutic food.

each RUTF group and age category, the daily energy intake did not differ between those who recovered and those who were discharged as nonrecovered (data not shown).

RUTF acceptability and tolerance

The data on RUTF acceptability suggested that the only difference between the 2 RUTF products was that fewer children aged <24 mo experienced flatulence while on the SMS-RUTF (Supplemental Table 6). Among those who defaulted, a dislike of the RUTF was reported in 19.2% (14/73) of the SMS-RUTF group compared with 13.3% (6/45) in the P-RUTF group ($P = 0.411$). Side effects related to RUTF intake were 2.74% (2/73) in

the SMS-RUTF group compared with 2.22% (2/45) in the P-RUTF group ($P = 0.862$).

DISCUSSION

Children with SAM need safe and palatable foods with energy, protein, fat, minerals, and vitamins tailored to their needs for restoring normal body functions and to catch up in growth (32). Providing P-RUTF tailored to body weight has been shown to successfully support catch-up growth (2, 44), but it is expensive, and the high cost affects the coverage and sustainability of CMAM programs. Almost half the cost of the P-RUTF is because

TABLE 4

Comparison of overnight-fasted concentrations of selected amino acids at baseline and discharge¹

Amino acid, $\mu\text{mol/L}$	Median (IQR)			Comparisons (P values) ²		
	Control ³ (A)	SMS-RUTF (B)	P-RUTF (C)	A vs. B	A vs. C	B vs. C
Admission, n	25	30	30			
Lysine	102.81 (87.49–142.21)	70.59 (44.08–102.99)	81.80 (43.92–112.06)	0.004	0.009	0.496
Valine	124.51 (103.47–161.08)	90.89 (57.23–113.46)	103.91 (75.59–125.41)	<0.001	0.008	0.117
Methionine	16.54 (13.27–20.30)	10.99 (7.22–15.27)	12.83 (10.18–15.05)	<0.001	0.004	0.178
Cystine	25.62 (20.73–28.58)	10.48 (6.49–16.98)	16.32 (9.08–21.29)	<0.001	<0.001	0.158
Tyrosine	45.61 (41.60–52.92)	22.35 (11.45–34.81)	30.36 (22.13–41.68)	<0.001	<0.001	0.209
Tryptophan	15.41 (7.66–19.20)	4.27 (2.50–9.28)	4.14 (2.23–9.62)	<0.001	0.003	0.685
Phenylalanine	47.22 (41.21–58.15)	37.67 (25.68–52.43)	39.94 (29.34–55.24)	0.030	0.063	0.469
Discharge, n	25	20	26			
Lysine	102.81 (87.49–142.21)	109.22 (85.67–144.31)	99.44 (84.81–144.84)	0.819	0.880	0.690
Valine	124.51 (103.47–161.08)	117.50 (98.27–139.60)	127.08 (103.98–159.80)	0.385	0.985	0.506
Methionine	16.54 (13.27–20.30)	13.61 (10.48–15.01)	14.56 (11.97–16.28)	0.005	0.048	0.268
Cystine	25.62 (20.73–28.58)	24.96 (16.70–34.08)	35.60 (29.00–39.04)	0.715	<0.001	0.004
Tyrosine	45.61 (41.60–52.92)	39.07 (30.36–54.77)	48.00 (41.54–71.04)	0.537	0.258	0.092
Tryptophan	15.41 (7.66–19.20)	13.24 (8.26–20.68)	20.13 (13.15–31.61)	0.784	0.024	0.092
Phenylalanine	47.22 (41.21–58.15)	39.72 (33.29–54.74)	43.57 (38.75–66.60)	0.144	0.638	0.215

¹P-RUTF, peanut paste-based ready-to-use therapeutic food; SMS-RUTF, soya-maize-sorghum ready-to-use therapeutic food.

²Mann-Whitney test with Bonferroni correction (difference statistically significant if $P < 0.017$).

³Community controls were surveyed only once, and the same data were used for comparing admission and discharge data.

TABLE 5
Between-group comparisons at discharge and with community controls of body composition variables measured by the deuterium dilution technique¹

Variables	Control (A) ² (n = 47)	SMS-RUTF (B) (n = 29)	P-RUTF (C) (n = 26)	B vs. A		C vs. A		B vs. C	
				Difference (95% CI)	P value	Difference (95% CI)	P value	Difference (95% CI)	P value
Age, mo	36.53 ± 18.7	40.75 ± 17.7	33.6 ± 19.0	4.2 (-4.4, 12.8)	0.332	-2.9 (-12.0, 6.3)	0.534	7.1 (-2.8, 17.0)	0.158
Weight, kg	11.5 ± 2.5	10 ± 2.1	9.2 ± 2.3	-1.5 (-2.6, -0.4)	0.010	-2.3 (-3.5, -1.1)	<0.001	0.8 (-0.4, 2.0)	0.174
Height, cm	84.5 ± 9.8	79.5 ± 8.6	77.1 ± 9.8	-5.0 (-9.7, -0.4)	0.033	-7.5 (-12.5, -2.5)	0.004	2.4 (-2.5, 7.4)	0.321
MUAC, cm	14.3 ± 1.2	13.3 ± 0.8	13.1 ± 0.7	-1.0 (-1.4, -0.4)	<0.001	-1.1 (-1.6, -0.6)	<0.001	0.2 (-0.2, 0.6)	0.260
WAZ	1.47 ± 0.94	-3.06 ± 0.79	-3.02 ± 0.94	-1.59 (-2.03, -1.15)	<0.001	-1.54 (-2.02, -1.07)	<0.001	-0.05 (-0.51, 0.42)	0.842
HAZ	-2.54 ± 1.48	-4.56 ± 0.85	-4.12 ± 1.45	-2.02 (-2.58, -1.45)	<0.001	-1.59 (-2.27, -0.90)	<0.001	-0.44 (-1.07, 0.20)	0.177
WHZ	0.02 ± 0.86	-0.44 ± 0.97	-0.77 ± 0.69	-0.46 (-0.88, -0.04)	0.033	-0.79 (-1.18, -0.40)	<0.001	0.33 (-0.13, 0.79)	0.157
Fat-free mass, kg	9.4 ± 2.6	8.1 ± 2.2	7.6 ± 1.8	-1.3 (-2.4, -0.1)	0.034	-1.8 (-2.9, -0.6)	0.003	0.5 (-0.6, 1.6)	0.341
Body fat mass, kg	2.1 ± 1.0	1.9 ± 0.9	1.6 ± 0.9	-0.2 (-0.7, 0.2)	0.374	-0.5 (-1.0, 0.0)	0.041	0.3 (-0.2, 0.8)	0.245
Fat, %	19.2 ± 9.2	19.7 ± 9.3	17.3 ± 7.3	0.5 (-3.9, 4.8)	0.825	-1.9 (-6.1, 2.3)	0.369	2.4 (-2.2, -7.0)	0.300
Fat-free mass index, ³ kg/m ²	12.9 ± 1.1	12.7 ± 1.7	12.6 ± 1.1	-0.2 (-0.8, 0.4)	0.535	-0.3 (-0.8, 0.2)	0.274	0.1 (-0.7, 0.9)	0.802
Fat mass index, ⁴ kg/m ²	3.1 ± 1.0	3.1 ± 1.5	2.7 ± 1.0	0.0 (-0.6, 0.6)	0.999	-0.4 (-0.9, 0.1)	0.111	0.4 (-0.3, 1.1)	0.262

¹Values are means ± SDs unless otherwise indicated. A *t* test with Bonferroni correction was used for the between-group comparisons (difference statistically significant if *P* < 0.017). HAZ, height-for-age z score; MUAC, midupper arm circumference; P-RUTF, peanut paste-based ready-to-use therapeutic food; SMS-RUTF, soya-maize-sorghum ready-to-use therapeutic food; WAZ, weight-for-age z score; WHZ, weight-for-height z score.

²Nonwasted children with no history of severe acute malnutrition were recruited to serve as community controls.

³Fat-free mass relative to height obtained by dividing the fat-free mass (in kg) by the height (in m).

⁴Body fat mass relative to height obtained by dividing the body fat mass (in kg) by the height (in m).

of milk powder, which constitutes 25–30% of the content of P-RUTF, and removing the milk powder from RUTF has the potential to substantially reduce the cost of such products. Although accurately predicting savings without undertaking actual commercial-scale trials is difficult, our analysis in Malawi, where the study foods were produced, suggests 15% savings on finished product cost. However, the savings are likely to vary from year to year according to the price of milk powder in local and global markets and to the country of production.

This study yielded important information regarding the efficacy of the nonmilk SMS-RUTF. We confirmed that SMS-RUTF is not inferior to P-RUTF in children aged ≥24 mo with respect to recovery rate, weight gain, and LOS and therefore can be used as an alternative to P-RUTF. We also showed that treatment with both SMS-RUTFs and P-RUTFs corrected amino acid deficiencies to a similar extent and that both RUTFs were not associated with an excess of fat deposition. **The BIA substudy confirmed substantial increases in the FFMI in both groups, bringing them back in line with the community controls.** In the SMS-RUTF group, the increase in FFMI was slightly less than in the P-RUTF group, corresponding to the greater increases in length seen in this group. This minor difference in FFMI was associated by a small difference that is unlikely to have any **clinical importance in the markers of FFM quality (PhA, IM)** that were also lower in the SMS-RUTF group; the greater increase in hemoglobin produced by SMS-RUTF than by P-RUTF also shows that it is possible to improve the efficacy of RUTF formulations in correcting anemia. We have also provided evidence that children aged <24 mo do not respond as well to SMS-RUTF and that P-RUTF should continue to be used for this age group until a cheaper alternative is developed.

The need of animal source food, especially of cow milk products, in food for managing acute malnutrition, including moderate and severe acute malnutrition, is still the subject of an ongoing debate (45–49). Several properties of milk, including the high quality of proteins, presence of bioactive factors, mineral profile, and high lactose content, are given as reasons for the obligatory inclusion of a certain amount of milk in RUTF (49). As a result, the current UN guidelines specify that >50% of the protein in RUTF should be from an animal source. However, several studies from industrialized countries have shown that in fast-growing infants, soya can successfully replace cow milk when there is a medical or sociocultural contraindication to milk (50). Similarly, a study published in 1996 showed that the effectiveness of soya and cow milk were similar in the nutritional rehabilitation of SAM (51), and we have previously demonstrated that it is possible to achieve the recommended nutrient profile for RUTF without including milk (52). This study confirms our previous findings from Zambia that an SMS-RUTF containing no animal source protein is as effective as P-RUTF in treating SAM in children aged ≥24 mo (11). This finding has important practical implications because it indicates that the cost of the CMAM programs can safely be reduced by using SMS-RUTF in all children aged ≥2 y and restricting the more expensive P-RUTF for use in children aged <2 y.

The reasons for the inferior response to the milk-free RUTF in children aged <2 y are not clear. They could be related to 1 or more factors, including differences in energy/nutrient intake, protein quality, the prevalence of lactose intolerance, the bioavailability of essential nutrients, or physiological responses

TABLE 6Between-group comparison of bioelectrical impedance analysis variables of children at admission and discharge¹

Variable	SMS-RUTF (n = 73)	P-RUTF (n = 90)	Difference (95% CI) ²	P value
Admission				
Age, mo	43.85 ± 11.74	42.38 ± 13.67	1.47 (−2.52, 5.46)	0.468
Weight, kg	9.12 ± 1.48	8.69 ± 1.50	0.43 (−0.04, 0.89)	0.071
Height, cm	81.69 ± 7.52	79.76 ± 7.33	1.93 (−0.37, 4.24)	0.1
MUAC, cm	11.7 ± 0.8	11.5 ± 0.8	0.2 (−0.0, 0.5)	0.057
Discharge				
Age, mo	45.94 ± 11.91	45.30 ± 14.97	0.64 (−3.62, 4.90)	0.767
Weight, kg	10.43 ± 1.53	10.46 ± 1.1.69	−0.03 (−0.53, 0.47)	0.902
Height, cm	82.41 ± 7.40	80.55 ± 7.28	1.86 (−0.41, 4.13)	0.109
MUAC, cm	13.4 ± 0.7	13.6 ± 0.8	−0.2 (−0.4, 0.0)	0.094
Fat-free mass, kg	8.50 ± 1.21	8.58 ± 1.11	−0.08 (−0.44, 0.29)	0.661
Fat mass, kg	1.93 ± 0.81	1.88 ± 0.78	0.05 (−0.21, 0.29)	0.69
Fat mass, %	17.6 ± 6.0	18.0 ± 6.0	−0.4 (−2.27, 1.47)	0.672
Fat-free mass index, ³ kg/m ²	12.7 ± 1.1	13.2 ± 1.1	−0.5 (−0.85, −0.15)	0.006
Fat mass index, ⁴ kg/m ²	2.74 ± 1.03	2.96 ± 1.17	−0.22 (−0.56, 0.13)	0.21
Phase angle, °	3.47 ± 0.51	3.74 ± 0.53	−0.26 (−0.43, −0.10)	0.002
Resistance, Ω	959 ± 91	923 ± 95	35 (7, 65)	0.016
Reactance, Ω	57.92 ± 10.32	60.33 ± 10.23	−2.41 (−5.60, 0.79)	0.138
Illness marker	0.957 ± 0.007	0.95 ± 0.013	0.006 (0.003, 0.009)	<0.001
Resistance:height, Ω/cm	1172 ± 151	1156 ± 166	15.66 (−34.98, 65.31)	0.534
Reactance:height, Ω/cm	70.47 ± 12.25	75.45 ± 14.42	−4.99 (−9.18, −0.79)	0.02

¹Values are means ± SDs unless otherwise indicated. MUAC, midupper arm circumference; P-RUTF, peanut paste-based ready-to-use therapeutic food; SMS-RUTF, soya-maize-sorghum ready-to-use therapeutic food.

²Difference estimated with the use of *t* test analysis.

³Fat-free mass relative to height obtained by dividing the fat-free mass (in kg) by the height (in m).

⁴Body fat mass relative to height obtained by dividing the body fat mass (in kg) by the height (in m).

between the 2 age groups. We believe that differences in energy intake are unlikely to be important. In a study of adults treated with a chickpea sesame RUTF that contained no milk or other animal source protein, there was an excellent correlation between RUTF intake, weight gain, and FFM change (53). By contrast, in this study there was no significant difference of daily intake between age groups, indicating that the poorer response was not the result of any reduction in the intake of energy. In children aged <2 y who did not recover, the mean RUTF intake was 133 kcal · kg^{−1} · d^{−1}. This energy intake, although lower than the recommended intake of 200 kcal · kg^{−1} · d^{−1}, should have been sufficient to cover basal metabolic requirements and allow for some growth and recovery. In addition, all these children were still breastfed, and it is likely that breast milk further contributed to their energy intake. The contribution of breast milk to their nutritional intake is unknown, however, because although evidence suggests that RUTF used for the prevention of malnutrition does not reduce breast milk intake, there are no data on whether this is true when RUTF is prescribed in much larger amounts for treatment (54).

Differences in protein quality between SMS-RUTF and P-RUTF combined with a greater requirement for certain amino acids in young children cannot be ruled out as a cause of the inferior response to the milk-free RUTF in children aged <2 y. SMS-RUTF had a lower content of tyrosine, methionine, and proline than P-RUTF. The mean daily SMS-RUTF intake in children discharged as nonrecovered corresponded to a daily intake of 121 mg · kg^{−1} · d^{−1} tyrosine and 52 mg · kg^{−1} · d^{−1} methionine. These intakes are greater than the 99 mg · kg^{−1} · d^{−1} tyrosine that Badaloo et al. (55) estimated was needed to support a catch-up growth of 15 g · kg^{−1} · d^{−1} and above the

38 mg · kg^{−1} · d^{−1} methionine required by formula-fed infants who grow at more than 10 g · kg^{−1} · d^{−1} (56). The increased plasma concentrations of free amino acids between admission and discharge and compared with those seen in community controls indicate that the 2 RUTFs supplied sufficient quantities of these amino acids. However, we did not measure all the amino acids, and the sample size did not allow testing a sufficient number of nonrecovered children. Thus, future research should still assess the possible contribution of some key amino acids in the poor physical growth in children aged <24 mo recovering from SAM.

A decreased bioavailability of essential nutrients is another possible cause for the inferior response to the milk-free RUTF in younger children. Phytic acid is a common plant storage compound not present in animal source foods that binds divalent metallic ions and prevents their absorption in the small intestine. It is therefore theoretically possible that the switch from milk to grains and legumes could have increased the phytic acid content of the SMS-RUTF, thus decreasing the bioavailability of iron and zinc. We believe, however, that this explanation is unlikely. A recent laboratory analysis of different P-RUTFs found huge variations in the phytic acid concentrations that ranged from 1015 mg/100 g for P-RUTF produced in Europe to 371 mg/100 g for P-RUTF manufactured in African countries (57). The iron content of 10–14 mg/100 g in the P-RUTF combined with these amounts of phytic acid give phytic acid:iron ratios between 7 and 13, far higher than the recommended upper limit ratio of <1 (58). By contrast, the production of SMS-RUTF included specific measures to reduce phytic acid and to increase iron content. This resulted in a phytic acid acid:iron ratio of 0.8. Based on evidence that increasing vitamin C improves the absorption of iron (59, 60), the

vitamin C content of the SMS-RUTF was also increased to enhance iron bioavailability. The greater increase in hemoglobin among children receiving SMS-RUTF suggests that these measures were effective in increasing iron absorption. The SMS-RUTF also included more zinc than did the P-RUTF to bring the phytic acid:zinc ratios toward international recommendations (see Table 1). Specific iron and zinc absorption studies should be conducted to confirm that the strategy used to improve the bioavailability of these minerals was sufficient.

Several studies have reported that lactose tolerance declines naturally with age, with the prevalence of lactose intolerance increasing sharply after the cessation of breastfeeding at around 24 mo (61, 62). Indeed, postweaning genetically programmed and irreversible reduction of lactase activity have been described worldwide (63). Thus, increasing lactose intolerance in older children could explain the differences seen with the benefit of the growth-promoting nutrients present in milk increasingly counterbalanced by the negative effect of lactose intolerance in older children. However, because the response to treatment in both study arms was superior among children aged ≥ 24 mo, this explanation is unlikely, a conclusion supported by the fact that several studies have previously reported a similar growth pattern in lactose-intolerant children given lactose-free dairy products compared with lactose-intolerant children given dairy products containing lactose (61, 62).

Differences in the pathophysiology of SAM between the 2 age groups is likely to be important in both the inferior response in the treatment of SAM and the different linear growth response of the younger and older children that we observed. In this study, the length for age in children aged <24 mo continued to decline during nutritional treatment, whereas in the older children some linear growth catch-up was observed during treatment. This suggests that the nutrient requirement for rehabilitation may not be the same for children of different ages, and it is likely that similar physiological differences are also important reasons behind the inferior response to the milk-free RUTF in the younger children. These findings highlight the need to enhance our understanding of the differences between younger and older SAM children, including differences in biochemical parameters, nutrient requirements, body composition at different stages of acute malnutrition, and the precise composition of weight gain at different times of the recovery process. Such information is likely to facilitate the adjustment of RUTF composition with the aim of developing a product capable of reversing both wasting and stunting, especially in children aged <24 mo.

In this study, there was a considerably greater increase in hemoglobin, with no evidence of increased morbidity from use of an RUTF with an iron content ~ 4 times greater than that currently recommended. This suggests a need to revise the current recommendation and increase iron density in RUTF. Historically, fears that iron might induce the formation of free radicals that could not be detoxified in children with SAM meant that the iron content of RUTF was kept low (64, 65). Additional concerns related to the promotion of pathogenic bacteria in the gut that some studies have attributed to iron-fortified food (66, 67) have served to keep the iron content of RUTF down (68–70). However, increasing iron concentrations in nutritional supplements has been shown to have positive effects on growth (71) and hemoglobin (72), and other studies have indicated that iron can be safely prescribed to children recovering from severe

malaria, a condition that in the past has been associated with a very high postdischarge mortality (73, 74). An unpublished study conducted in Senegal also showed that during the treatment of SAM with P-RUTF containing the current recommended iron density, hemoglobin went up by 0.17 g/dL compared with an increase of 0.83 g/dL in those receiving F-100 therapeutic milk fortified with iron to provide $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ (HIE Diop, NI Dossou, MM Ndour, A Briend, S Wade, unpublished data). It is important to note that even at the increased iron dosage used in the SMS-RUTF there was still a high proportion of anemic children at discharge, and it is likely that any solution to the problems of anemia in SAM will require a mechanism to increase iron intake for several months post-discharge.

This is the first study to our knowledge to use the reference 2 compartments modeling technique for determining body composition (DDT approach), showing that the use of RUTF for nutritional rehabilitation of SAM children is not associated with an excess deposition of fat. All previous studies that evaluated this issue were done in a program treating SAM children with the use of a milk-based diet (75–77). These studies showed that nutritional therapy with an appropriately fortified milk diet is not associated with excesses in fat mass deposition (75–77). However, despite these studies, the debate has continued around the possible association between rapid weight catch-up growth observed during nutritional rehabilitation of SAM and higher amounts of body fat deposition and insufficient repletion of muscle and visceral proteins (77–81). We showed no excess fat deposition either with SMS-RUTF or with P-RUTF compared with community controls, and at the time of discharge the absolute fat mass in children who had met anthropometric discharge criteria was similar to community controls. These results confirm the findings of a recently published study conducted in Kampala, Uganda, that, through the use of serum leptin concentration as a proxy biomarker of fat reserves, demonstrated that fat replenishment is completed first and early during nutritional rehabilitation, before the anthropometric discharge criteria are met (82).

Our results also show that at the time these children meet anthropometric criteria for recovery they still have deficits of FFM compared with the community controls, indicating that current best-practice SAM treatment regimens combined with the use of the internationally accepted discharge criteria are not necessarily sufficient for reestablishing FFM. This important finding provides a rationale for the persistent increased risk of death in children who are treated and anthropometrically “cured” in tertiary hospitals after admission at an advanced stage of wasting and metabolic adaptation (83, 84). It also perhaps helps to explain the much lower long-term mortality risk after discharge of those admitted to community-based programs at an earlier stage in the progression of SAM (83).

In this study, the FM and FFM of children who recovered were comparable to those of the community controls, suggesting that the differences in the absolute amounts of FFM could be explained by differences in height. It is therefore possible that the residual increased risk of mortality after being treated for SAM and discharged may be related to the degree of stunting (85). The close interconnections between acute and chronic malnutrition combined with the relatively limited impact of a short-duration treatment with RUTF on stunting support the need of



investigating integrated approaches toward acute and chronic malnutrition (86–88). Such approaches that combine intensive initial nutritional rehabilitation to correct weight/muscle deficit and prolonged nutritional support to reestablish FFM and sustain linear deficit recovery should be developed, and their effectiveness in preventing relapse and promoting linear growth and FFM catch-ups should be assessed.

BIA analysis yielded similar results to DDT regarding changes in body fat, FFM, and FFMI. In addition, the BIA analysis identified considerable differences in cellular membrane function indicators such as phase angle and illness marker between children treated with SMS-RUTF and those treated with P-RUTF. The clinical importance of the observed differences is unknown and needs to be further investigated, but many studies have demonstrated that phase angle is an independent predictor of diseases and death in both children and adults (89–93).

This study was conducted in a setting where all the ingredients were already commonly used in the preparation of porridge for complementary feeding. Despite that, our findings can be generalized because soya and maize have been used in food distributed during humanitarian crises worldwide, and existing evidence shows that the standard RUTF is effective in children aged 6–59 mo suffering from SAM of all continents, even where peanut paste is not commonly used in feeding infant and young children. In addition, we enrolled children with the use of criteria universally used for enrollment in CMAM programs. However, our findings should not be interpreted without taking into account some limitations. The main limitation is that we could not measure the total daily nutritional intake and thus measured only RUTF intake instead. Measuring total daily intake would have allowed us to better distinguish the effect of product composition on satiety on the response observed in both age groups. Although we doubt that the intake from home food or breast milk influenced the recovery, we could not exclude it definitively. The second limitation is that we could not include a sufficient number of children who did not recover in the substudies evaluating the evolution of amino acid profile or assessing body composition to determine whether differences in food quality such as in amino acid profile contributed to the differences observed.

In conclusion, we demonstrated that SMS-RUTF can be used to treat SAM in children aged ≥ 24 mo and that the iron content in RUTF should be increased. The lower cost of manufacturing SMS-RUTF and its reliance on locally grown ingredients would reduce the costs of CMAM programs and facilitate the production of RUTF in countries with a high burden of SAM, especially because we have placed this recipe in the public domain and put in place mechanisms preventing any entity from blocking access to it. The additional iron would increase the efficacy of the product in the treatment of anemia associated with SAM.

We have also shown that there is a need for 2 products with different compositions to treat SAM: one for children aged < 2 y that ideally should also be optimized to promote a reversal of stunting, and one for children aged > 2 y that should be formulated to maintain efficacy but reduce costs. Cost-effectiveness analyses and the assessment of the impact on program logistics are needed to guide the final decision. More research is required to identify the reasons for the lower recovery rate with SMS-RUTF in younger children. Hypotheses to be explored include higher satiety with SMS-RUTF, lower breast milk intake, sub-optimal absorption of some key micronutrients, and differences

in key amino acids. More research is also needed on products that better address stunting in this younger age group.

We thank Julien Mubalama Katembo Namudukuza and Nicolas Kashama of the MMHZ management team for their support.

The authors' responsibilities were as follows—PB, KS, PA, and SC: conceived the study idea, designed the SMS-RUTF, and provided technical oversight throughout the trial, including collecting and analyzing data and preparing the manuscript; BB and CNM: contributed to the study design and data collection tools development and implemented data collection and entry; JCKW and MD-W: participated in the analysis of the data and the interpretation of findings; and all authors: read and approved the final manuscript. Valid Nutrition designed and produced the SMS-RUTF. PA is an employee of Valid Nutrition. SC is the unpaid director of Valid Nutrition. Valid International is the sister company of Valid Nutrition, and BP and KS are Valid International employees. None of the others authors reported a conflict of interest related to this study. The PRANA Foundation and Irish Aid had no input on the design, implementation, and interpretation of the results. Valid Nutrition administered the study grant. Valid Nutrition and Valid International researchers participated in the study design and implementation and in the interpretation of results.

REFERENCES

1. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* 2013;382:427–51.
2. Collins S, Dent N, Binns P, Bahwere P, Sadler K, Hallam A. Management of severe acute malnutrition in children. *Lancet* 2006;368:1992–2000.
3. Collins S. Community-based therapeutic care: a new paradigm for selective feeding in nutritional crises. Network paper. London: Humanitarian Practice Network; 2004.
4. Bahwere P, Piwoz E, Joshua MC, Sadler K, Grobler-Tanner CH, Guerrero S, Collins S. Uptake of HIV testing and outcomes within a community-based therapeutic care (CTC) programme to treat severe acute malnutrition in Malawi: a descriptive study. *BMC Infect Dis* 2008;8:106.
5. Briend A, Lacsala R, Prudhon C, Mounier B, Grellety Y, Golden MHN. Ready-to-use therapeutic food for treatment of marasmus. *Lancet* 1999;353:1767–8.
6. Manary MJ. Local production and provision of ready-to-use therapeutic food (RUTF) spread for the treatment of severe childhood malnutrition. *Food Nutr Bull* 2006;27:S83–9.
7. WHO. Management of severe malnutrition: a manual for physicians and other senior health workers. Geneva (Switzerland): WHO; 1999.
8. Rogers E, Myatt M, Woodhead S, Guerrero S, Alvarez JL. Coverage of community-based management of severe acute malnutrition programmes in twenty-one countries, 2012–2013. *PLoS One* 2015;10:e0128666.
9. Collins S, Sadler K. Outpatient care for severely malnourished children in emergency relief programmes: a retrospective cohort study. *Lancet* 2002;360:1824–30.
10. Diop HI, Dossou NI, Ndour MM, Briend A, Wade S. Comparison of the efficacy of a solid ready to use food and a liquid milk-based diet for the rehabilitation of severely malnourished children: a randomized trial. *Am J Clin Nutr* 2003;78:302–7.
11. Irena AH, Bahwere P, Owino VO, Diop EI, Bachmann MO, Mbwili-Muleya C, Dibari F, Sadler K, Collins S. Comparison of the effectiveness of a milk-free soy-maize-sorghum-based ready-to-use therapeutic food to standard ready-to-use therapeutic food with 25% milk in nutrition management of severely acutely malnourished Zambian children: an equivalence non-blinded cluster randomised controlled trial. *Matern Child Nutr* 2015;11(Suppl 4):105–19.
12. Action Against Hunger. Enquête Nutritionnelle Anthropométrique: zone de santé de Miti-Murhesa. [Nutritional Anthropometric Study: health zone Miti-Murhesa.] [Internet]. [cited 2012 Jun 12]. New York: Action Against Hunger; 2011. Available from: http://www.actionagainsthunger.org/sites/default/files/publications/Enquete_Nutritionnelle_Anthropometrique_Zone_de_Sante_de_Miti-Murhesa_Province_du_Sud-Kivu_DRC_08.2011.pdf (in French).

13. Balaluka GB, Nabugobe PS, Mitangala PN, Cobohwa NB, Schirvel C, Dramaix MW, Donnen P. Community volunteers can improve breast-feeding among children under six months of age in the Democratic Republic of Congo crisis. *Int Breastfeed J* 2012;7:2.
14. Bisimwa G, Mambo T, Mitangala P, Schirvel C, Porignon D, Dramaix M, Donnen P. Nutritional monitoring of preschool-age children by community volunteers during armed conflict in the Democratic Republic of the Congo. *Food Nutr Bull* 2009;30:120–7.
15. Vis HL, Pourbaix P, Thilly C, Van der Borgh H. Analyse de la situation nutritionnelle des traditional sociétés de la région du lac Kivu: la Shi et l'Havu. Étude de la consommation alimentaire. [Analysis of the nutritional situation of traditional societies of the Kivu Lake region: the Shi and the Havu. Study of food consumption.] *Ann Soc Belges Med Trop Parasitol Mycol* 1969;49:353–419 (in French).
16. Nicoll A. Integrated management of childhood illness in resource-poor countries: an initiative from the World Health Organization. *Trans R Soc Trop Med Hyg* 2000;94:9–11.
17. Democratic Republic of Congo, Ministry of Health. Protocole national de prise en charge intégrée de la malnutrition aiguë. [National Protocol for the Integrated Management of Acute Malnutrition.] [Internet]; 2011. [cited 2013 Oct 6]. Available from: http://reliefweb.int/sites/reliefweb.int/files/resources/Situation_Report_258.pdf (in French).
18. WHO. Training course on child growth assessment. Geneva (Switzerland): WHO; 2008.
19. Bertani R, Sergi G, Lupoli L, Berton A, Volpato S, Zambon K, Coin A, Enzi G. Measurement of total body water (TBW) through in vivo dilution of tracer compounds: use of D2O and its determination by FT infrared spectroscopy. *Ann Chim* 2002;92:135–8.
20. Girma T, Kaestel P, Workeneh N, Molgaard C, Andersen GS, Michaelsen KF, Friis H, Wells JC. Biopédance index for measurement of total body water in severely malnourished children: assessing the effect of nutritional oedema. *Clin Nutr* 2015 July 10 (Epub ahead of print; DOI: 10.1016/j.clnu.2015.05.002).
21. Fomon SJ, Haschke F, Ziegler EE, Nelson SE. Body composition of reference children from birth to age 10 years. *Am J Clin Nutr* 1982;35:1169–75.
22. Imaizumi A, Shimba N, Yoshida H, Miyano H, Yoneda J, Nagao K, Nishikata N, Takahena S, Takahashi M, Kimura T. Clinical implementation of metabolomics. INTECH Open Access Publisher: Rijeka (Croatia); 2012.
23. Yoshida H, Kondo K, Yamamoto H, Kageyama N, Ozawa S, Shimbo K, Muramatsu T, Imaizumi A, Mizukoshi T, Masuda J, et al. Validation of an analytical method for human plasma free amino acids by high-performance liquid chromatography ionization mass spectrometry with use of automated precolumn derivatization. *J Chromatogr B Analyt Technol Biomed Life Sci* 2015;998-999:88–96.
24. Bahwere P, Deconinck H, Banda T, Mtumini A, Collins S. Impact of household food insecurity on the nutritional status and the response to therapeutic feeding of people living with human immunodeficiency virus. *Patient Prefer Adherence* 2011;5:619–27.
25. Bahwere P, Banda T, Sadler K, Nyirenda G, Owino V, Shaba B, Dibari F, Collins S. Effectiveness of milk whey protein-based ready-to-use therapeutic food in treatment of severe acute malnutrition in Malawian under-5 children: a randomised, double-blind, controlled non-inferiority clinical trial. *Matern Child Nutr* 2014;10:436–51.
26. Bahwere P, Deconinck H, Banda T, Collins S. Effective therapeutic feeding with chickpea sesame based ready-to-use therapeutic Food (CS-RUTF) in wasted adults with confirmed or suspected AIDS. *WORLD* 2011;1:169–81.
27. Kerac M, Bunn J, Seal A, Thindwa M, Tomkins A, Sadler K, Bahwere P, Collins S. Probiotics and prebiotics for severe acute malnutrition (PRONUT study): a double-blind efficacy randomised controlled trial in Malawi. *Lancet* 2009;374:136–44.
28. Flax VL, Maleta K, Ashorn U, Manary MJ, Briand A, Ashorn P. Intake of lipid-based nutrient supplements during illness and convalescence among moderately-underweight Malawian children. *J Health Popul Nutr* 2008;26:468–70.
29. Kayira D, Bentley ME, Wiener J, Mkhomawanthu C, King CC, Chitsulo P, Chigwenembe M, Ellington S, Hosseinipour MC, Kourtis AP, et al. A lipid-based nutrient supplement mitigates weight loss among HIV-infected women in a factorial randomized trial to prevent mother-to-child transmission during exclusive breastfeeding. *Am J Clin Nutr* 2012;95:759–65.
30. Parker ME, Bentley ME, Chasela C, Adair L, Piwoz EG, Jamieson DJ, Ellington S, Kayira D, Soko A, Mkhomawanthu C, et al. The acceptance and feasibility of replacement feeding at 6 months as an HIV prevention method in Lilongwe, Malawi: results from the BAN study. *AIDS Educ Prev* 2011;23:281–95.
31. Gibson RS, Bailey KB, Gibbs M, Ferguson EL. A review of phytate, iron, zinc, and calcium concentrations in plant-based complementary foods used in low-income countries and implications for bio-availability. *Food Nutr Bull* 2010;31:S134–46.
32. WHO/UNICEF/World Food Programme/UN System Standing Committee on Nutrition. Joint statement on the community-based management of severe malnutrition in children. [Internet]. 2007. [cited 2012 Jun 12]. Available from: http://apps.who.int/iris/bitstream/10665/44295/1/9789280641479_eng.pdf?ua=1&ua=1.
33. Schwartz J, Dube K, Sichert-Hellert W, Kannenberg F, Kunz C, Kalhoff H, Kersting M. Modification of dietary polyunsaturated fatty acids via complementary food enhances n-3 long-chain polyunsaturated fatty acid synthesis in healthy infants: a double blinded randomised controlled trial. *Arch Dis Child* 2009;94:876–82.
34. Pereira DI, Irving SSC, Lomer MC, Powell JJ. A rapid, simple questionnaire to assess gastrointestinal symptoms after oral ferrous sulphate supplementation. *BMC Gastroenterol* 2014;14:103.
35. Nyeko R, Kalyesubula I, Mworozzi E, Bachou H. Lactose intolerance among severely malnourished children with diarrhoea admitted to the nutrition unit, Mulago hospital, Uganda. *BMC Pediatr* 2010;10:31.
36. Sealed Envelope Ltd. Power calculator for binary outcome non-inferiority trial. [Internet]. [cited 2012 May 5]. Available from: <https://www.sealedenvelope.com/power/binary-noninferior>.
37. Julious SA. Sample sizes for clinical trials with normal data. *Stat Med* 2004;23:1921–86.
38. Julious SA, Campbell MJ. Tutorial in biostatistics: sample sizes for parallel group clinical trials with binary data. *Stat Med* 2012;31:2904–36.
39. Lauritsen JM, Bruus M. EpiData entry version 3.02: a comprehensive tool for validated entry and documentation of data (3.02). Odense (Denmark): EpiData Association; 2003.
40. StataCorp. Stata statistical software: release 12. College Station (TX): StataCorp; 2011.
41. Bozzetto S, Piccoli A, Montini G. Bioelectrical impedance vector analysis to evaluate relative hydration status. *Pediatr Nephrol* 2010;25:329–34.
42. Le Henanff A, Giraudeau B, Baron G, Ravaud P. Quality of reporting of noninferiority and equivalence randomized trials. *JAMA* 2006;295:1147–51.
43. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006;295:1152–60.
44. Collins S, Sadler K, Dent N, Khara T, Guerrero S, Myatt M, Saboya M, Walsh A. Key issues in the success of community-based management of severe malnutrition. *Food Nutr Bull* 2006;27:S49–82.
45. Ferguson EL, Briand A, Darmon N. Can optimal combinations of local foods achieve the nutrient density of the F100 catch-up diet for severe malnutrition? *J Pediatr Gastroenterol Nutr* 2008;46:447–52.
46. Golden BE, Golden MH. Plasma zinc, rate of weight gain, and the energy cost of tissue deposition in children recovering from severe malnutrition on a cow's milk or soya protein based diet. *Am J Clin Nutr* 1981;34:892–9.
47. Hoppe C, Andersen GS, Jacobsen S, Molgaard C, Friis H, Sangild PT, Michaelsen KF. The use of whey or skimmed milk powder in fortified blended foods for vulnerable groups. *J Nutr* 2008;138:145S–61S.
48. Michaelsen KF, Hoppe C, Roos N, Kaestel P, Stougaard M, Lauritsen L, Molgaard C, Girma T, Friis H. Choice of foods and ingredients for moderately malnourished children 6 months to 5 years of age. *Food Nutr Bull* 2009;30:S343–404.
49. Michaelsen KF, Nielsen AL, Roos N, Friis H, Molgaard C. Cow's milk in treatment of moderate and severe undernutrition in low-income countries. *Nestle Nutr Workshop Ser Pediatr Program* 2011;67:99–111.
50. Vandenplas Y, Castrellon PG, Rivas R, Gutierrez CJ, Garcia LD, Jimenez JE, Anzo A, Hegar B, Alarcon P. Safety of soya-based infant formulas in children. *Br J Nutr* 2014;111:1340–60.
51. de Oliveira JE, Scatena L, Netto NO, Duarte GG. The nutritive value of soya milk and cow's milk in malnourished children: a comparative study. *J Pediatr* 1966;69:670–5.

52. Dibari F, Diop el HI, Collins S, Seal A. Low-cost, ready-to-use therapeutic foods can be designed with use of locally available commodities with the aid of linear programming. *J Nutr* 2012;142:955–61.
53. Bahwere P, Sadler K, Collins S. Acceptability and effectiveness of chickpea sesame-based ready-to-use therapeutic food in malnourished HIV-positive adults. *Patient Prefer Adherence* 2009;3:67–75.
54. Owino VO, Bahwere P, Bisimwa G, Mwangi CM, Collins S. Breast-milk intake of 9-10-mo-old rural infants given a ready-to-use complementary food in South Kivu, Democratic Republic of Congo. *Am J Clin Nutr* 2011;93:1300–4.
55. Badaloo A, Hsu JW, Taylor-Bryan C, Reid M, Forrester T, Jahoor F. Tyrosine requirement during the rapid catch-up growth phase of recovery from severe childhood undernutrition. *Br J Nutr* 2010;104:1174–80.
56. Huang L, Hogewind-Schoonenboom JE, van Dongen MJ, de Groof F, Voortman GJ, Schierbeek H, Twisk JW, Vermes A, Chen C, Huang Y, et al. Methionine requirement of the enterally fed term infant in the first month of life in the presence of cysteine. *Am J Clin Nutr* 2012;95:1048–54.
57. Roos N, Sorensen JC, Sorensen H, Rasmussen SK, Briend A, Yang Z, Huffman SL. Screening for anti-nutritional compounds in complementary foods and food aid products for infants and young children. *Matern Child Nutr* 2013;9:47–71.
58. Hurrell RF. Phytic acid degradation as a means of improving iron absorption. *Int J Vitam Nutr Res* 2004;74:445–52.
59. Troesch B, Egli I, Zeder C, Hurrell RF, Zimmermann MB. Fortification iron as ferrous sulfate plus ascorbic acid is more rapidly absorbed than as sodium iron EDTA but neither increases serum nontransferrin-bound iron in women. *J Nutr* 2011;141:822–7.
60. Cercamondi CI, Egli IM, Mitchikpe E, Tossou F, Hessou J, Zeder C, Hounhouigan JD, Hurrell RF. Iron bioavailability from a lipid-based complementary food fortificant mixed with millet porridge can be optimized by adding phytase and ascorbic acid but not by with use of a mixture of ferrous sulfate and sodium iron EDTA. *J Nutr* 2013;143:1233–9.
61. Erinoso HO, Hoare S, Spencer S, Lunn PG, Weaver LT. Is cow's milk suitable for the dietary supplementation of rural Gambian children? 1. Prevalence of lactose maldigestion. *Ann Trop Paediatr* 1992;12:359–65.
62. Brown KH, Parry L, Khatun M, Ahmed G. Lactose malabsorption in Bangladeshi village children: relation with age, history of recent diarrhea, nutritional status, and breast feeding. *Am J Clin Nutr* 1979;32:1962–9.
63. Wang Y, Harvey CB, Hollox EJ, Phillips AD, Poulter M, Clay P, Walker-Smith JA, Swallow DM. The genetically programmed down-regulation of lactase in children. *Gastroenterology* 1998;114:1230–6.
64. Dempster WS, Sive AA, Rosseau S, Malan H, Heese HV. Misplaced iron in kwashiorkor. *Eur J Clin Nutr* 1995;49:208–10.
65. Golden MHN, Ramdath D. Free radicals in the pathogenesis of kwashiorkor. *Proc Nutr Soc* 1987;46:53–68.
66. Soofi S, Cousens S, Iqbal SP, Akhund T, Khan J, Ahmed I, Zaidi AK, Bhutta ZA. Effect of provision of daily zinc and iron with several micronutrients on growth and morbidity among young children in Pakistan: a cluster-randomised trial. *Lancet* 2013;382:29–40.
67. Zimmermann MB, Chassard C, Rohner F, N'goran EK, Nindjin C, Dostal A, Utzinger J, Ghattas H, Lacroix C, Hurrell RF. The effects of iron fortification on the gut microbiota in African children: a randomized controlled trial in Cote d'Ivoire. *Am J Clin Nutr* 2010;92:1406–15.
68. Bernal C, Velasquez C, Alcaraz G, Botero J. Treatment of severe malnutrition in children: experience in implementing the World Health Organization guidelines in Turbo, Colombia. *J Pediatr Gastroenterol Nutr* 2008;46:322–8.
69. Golden MH. Proposed recommended nutrient densities for moderately malnourished children. *Food Nutr Bull* 2009;30:S267–342.
70. Jayatissa R, Bekele A, Kethiswaran A, De Silva AH. Community-based management of severe and moderate acute malnutrition during emergencies in Sri Lanka: challenges of implementation. *Food Nutr Bull* 2012;33:251–60.
71. Troesch B, van Stuijvenberg ME, Smuts CM, Kruger HS, Biebinger R, Hurrell RF, Baumgartner J, Zimmermann MB. A micronutrient powder with low doses of highly absorbable iron and zinc reduces iron and zinc deficiency and improves weight-for-age Z-scores in South African children. *J Nutr* 2011;141:237–42.
72. Lopriore C, Guidum Y, Briend A, Branca F. Spread fortified with vitamins and minerals induces catch-up growth and eradicates severe anemia in stunted refugee children aged 3–6 y. *Am J Clin Nutr* 2004;80:973–81.
73. Glinz D, Kamiyango M, Phiri KS, Munthali F, Zeder C, Zimmermann MB, Hurrell RF, Wegmüller R. The effect of timing of iron supplementation on iron absorption and haemoglobin in post-malaria anaemia: a longitudinal stable isotope study in Malawian toddlers. *Malar J* 2014;13:397.
74. Phiri KS, Calis JC, Faragher B, Nkhoma E, Ng'oma K, Mangochi B, Molyneux ME, van Hensbroek MB. Long term outcome of severe anaemia in Malawian children. *PLoS One* 2008;3:e2903.
75. Branca F, Robins SP, Ferro-Luzzi A, Golden MHN. Bone turnover in malnourished children. *Lancet* 1992;340:1493–6.
76. Fjeld CR, Schoeller DA, Brown KH. Body composition of children recovering from severe protein-energy malnutrition at two rates of catch-up growth. *Am J Clin Nutr* 1989;50:1266–75.
77. Radhakrishna KV, Kulkarni B, Balakrishna N, Rajkumar H, Omkar C, Shatrugna V. Composition of weight gain during nutrition rehabilitation of severely under nourished children in a hospital based study from India. *Asia Pac J Clin Nutr* 2010;19:8–13.
78. Castilla-Serna L, Perez-Ortiz B, Cravioto J. Patterns of muscle and fat mass repair during recovery from advanced infantile protein-energy malnutrition. *Eur J Clin Nutr* 1996;50:392–7.
79. Golden MH, Golden BE. Effect of zinc supplementation on the dietary intake, rate of weight gain, and energy cost of tissue deposition in children recovering from severe malnutrition. *Am J Clin Nutr* 1981;34:900–8.
80. Graham GG, MacLean WC Jr., Brown KH, Morales E, Lembcke J, Gastanaduy A. Protein requirements of infants and children: growth during recovery from malnutrition. *Pediatrics* 1996;97:499–505.
81. Spady DW, Payne PR, Picou D, Waterlow JC. Energy balance during recovery from malnutrition. *Am J Clin Nutr* 1976;29:1073–88.
82. Bartz S, Mody A, Hornik C, Bain J, Muehlbauer M, Kiyimba T, Kiboneka E, Stevens R, Bartlett J, Peter JVS. Severe acute malnutrition in childhood: hormonal and metabolic status at presentation, response to treatment, and predictors of mortality. *J Clin Endocrinol Metab* 2014;99:2128–37.
83. Bahwere P, Mtumuni A, Sadler K, Banda T, Collins S. Long term mortality after community and facility based treatment of severe acute malnutrition: analysis of data from Bangladesh, Kenya, Malawi and Niger. *J Public Health Epidemiol* 2012;4:215–25.
84. Kerac M, Bunn J, Chagaluka G, Bahwere P, Tomkins A, Collins S, Seal A. Follow-up of post-discharge growth and mortality after treatment for severe acute malnutrition (FuSAM Study): a prospective cohort study. *PLoS One* 2014;9:e96030.
85. Briend A, Khara T, Dolan C. Wasting and stunting—similarities and differences: policy and programmatic implications. *Food Nutr Bull* 2015;36(1 Suppl):S15–23.
86. Briend A, Garenne M, Maire B, Fontaine O, Dieng K. Nutritional status, age and survival: the muscle mass hypothesis. *Eur J Clin Nutr* 1989;43:715–26.
87. Heymsfield SB, Stevens V, Noel R, McManus C, Smith J, Nixon D. Biochemical composition of muscle in normal and semistarved human subjects: relevance to anthropometric measurements. *Am J Clin Nutr* 1982;36:131–42.
88. Khara, T, Dolan, C. Technical briefing paper: the relationship between wasting and stunting, policy, programming and research implications. Oxford (United Kingdom): Emergency Nutrition Network; 2014.
89. Gupta D, Lammersfeld CA, Burrows JL, Dahlk SL, Vashi PG, Grutsch JF, Hoffman S, Lis CG. Bioelectrical impedance phase angle in clinical practice: implications for prognosis in advanced colorectal cancer. *Am J Clin Nutr* 2004;80:1634–8.
90. Wells JC, Williams JE, Fewtrell M, Singhal A, Lucas A, Cole TJ. A simplified approach to analysing bio-electrical impedance data in epidemiological surveys. *Int J Obes (Lond)* 2007;31:507–14.
91. Richter E, Denecke A, Klapdor S, Klapdor R. Parenteral nutrition support for patients with pancreatic cancer—improvement of the nutritional status and the therapeutic outcome. *Anticancer Res* 2012;32:2111–8.
92. Lee SY, Lee YJ, Yang JH, Kim CM, Choi WS. The association between phase angle of bioelectrical impedance analysis and survival time in advanced cancer patients: preliminary study. *Korean J Fam Med* 2014;35:251–6.
93. Norman K, Stobaus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis: clinical relevance and applicability of impedance parameters. *Clin Nutr* 2012;31:854–61.