

Efficacy of three feeding regimens for home-based management of children with uncomplicated severe acute malnutrition: a randomised trial in India

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ABSTRACT

Objective: To assess the efficacy of ready-to-use therapeutic food (RUTF), centrally produced RUTF (RUTF-C) or locally prepared RUTF (RUTF-L) for home-based management of uncomplicated severe acute malnutrition (SAM) compared with micronutrient-enriched (augmented) energy-dense home-prepared foods (A-HPF, the comparison group).

Methods: In an individually randomised multicentre trial, we enrolled 906 children aged 6–59 months with uncomplicated SAM. The children enrolled were randomised to receive RUTF-C, RUTF-L or A-HPF. We provided foods, counselling and feeding support until recovery or 16 weeks, whichever was earlier and measured outcomes weekly (treatment phase). We subsequently facilitated access to government nutrition services and measured outcomes once 16 weeks later (sustenance phase). The primary outcome was recovery during treatment phase (weight-for-height ≥ -2 SD and absence of oedema of feet).

Results: Recovery rates with RUTF-L, RUTF-C and A-HPF were 56.9%, 47.5% and 42.8%, respectively. The adjusted OR was 1.71 (95% CI 1.20 to 2.43; $p=0.003$) for RUTF-L and 1.28 (95% CI 0.90 to 1.82; $p=0.164$) for RUTF-C compared with A-HPF. Weight gain in the RUTF-L group was higher than in the A-HPF group (adjusted difference 0.90 g/kg/day, 95% CI 0.30 to 1.50; $p=0.003$). Time to recovery was shorter in both RUTF groups. Morbidity was high and similar across groups. At the end of the study, the proportion of children with weight-for-height Z-score (WHZ) > -2 was similar (adjusted OR 1.12, 95% CI 0.74 to 1.95; $p=0.464$), higher for moderate malnutrition (WHZ < -2 and ≥ -3 ; adjusted OR 1.46, 95% CI 1.02 to 2.08; $p=0.039$), and lower for those with SAM (adjusted OR 0.58, 95% CI 0.40 to 0.85; $p=0.005$) in the RUTF-L when compared with the A-HPF group.

Conclusions: This first randomised trial comparing options for home management of uncomplicated SAM

Key questions

What is already known about this topic?

- Pooled analysis of three quasi-randomised controlled trials in Malawi, which evaluated ready-to-use therapeutic food (RUTF) in the home management of children with uncomplicated severe acute malnutrition (SAM) compared with standard diets, revealed that RUTF was associated with higher recovery rates (risk ratio 1.32, 95% CI 1.16 to 1.50).
- A Cochrane review concluded that given the limited evidence, it is not possible to reach definitive conclusions regarding differences in clinical outcomes in children with SAM who were given RUTF compared with standard diets.

What are the new findings?

- This first randomised trial comparing RUTF with energy and nutrient-dense home-prepared foods (the comparison group) confirms the efficacy of RUTF in the treatment of children with uncomplicated SAM.
- The study provides insights on the importance of feeding efforts and the caregiver support required for higher efficacy and highlights the importance of adequate continued inputs after initial treatment to sustain the benefits.

Recommendations for policy

- Children with uncomplicated SAM can be managed at home with RUTF instead of through inpatient hospitalisation.

confirms that RUTF-L is more efficacious than A-HPF at home. Recovery rates were lower than in African studies, despite longer treatment and greater support for feeding.

Trial registration number: NCT01705769; Pre-results.

INTRODUCTION

Severe acute malnutrition (SAM), defined as weight-for-height Z-score (WHZ) < -3 SD, markedly increases risk of mortality in under-5 children.¹ Annually, 0.5–2.0 million deaths are attributed to SAM.² Of the 20 million children with SAM worldwide, over eight million are from India, where around 5% of under-5 children suffer from SAM.^{2–4}

With a standardised hospital-based management protocol proposed by the WHO, recovery rates of around 80% have been reported and case fatality rates ranged between 3.4% and 35%.^{5–7} A very small proportion of children suffering from SAM receive effective management in India. Families seek medical care only when children with SAM have complications. They are reluctant to accept long hospital stay due to, for example, loss of wages and no arrangements at home to take care of other siblings. Perceptions that the disease is not severe enough to warrant long hospitalisation, the fear of hospitals, past experiences that were unpleasant and the cost of hospital care are also contributory factors.^{2 8–10}

Home-based management after initial hospitalisation was proposed for children with SAM as an effective strategy to increase coverage.¹⁰ This was supported by the development of ready-to-use therapeutic food (RUTF).^{8 11} Studies in Africa showed that, for home-based management of uncomplicated SAM, RUTF achieved recovery rates similar to those with hospital-based management.^{12–16}

Since 2007, the WHO recommends RUTF for home-based management of uncomplicated SAM.¹⁷ However, acceptance of this recommendation has been limited in countries like India. An important reason for the reluctance is the lack of evidence from controlled trials of the efficacy of RUTF compared with other treatment options. Experts have also questioned the ‘standardised diets’ used in studies. They argue that the comparison group should be given locally produced foods high in energy and proteins with adequate micronutrients.^{18–20} In addition, there are questions in India about the use of commercially produced RUTF over locally produced ‘analogous medical nutrition therapy’ or augmented home foods. Locally produced RUTF using indigenous foods may be less expensive and more sustainable if its efficacy could be proved.¹⁹ Reviews, including the most recent Cochrane review (2013), recommend well-designed, adequately powered, pragmatic randomised trials to compare treatment options for home-based management of uncomplicated SAM.^{19 21} A policy review in India reached a similar conclusion.²²

We therefore conducted a randomised trial to compare the efficacy of centrally produced RUTF (RUTF-C) and locally prepared RUTF (RUTF-L) for home-based management of children with uncomplicated SAM on recovery rates compared with micronutrient-enriched (augmented) energy-dense home-prepared foods (A-HPF), the comparison group.

METHODS

Study design

In this randomised trial, children aged 6–59 months with uncomplicated SAM were randomised into one of the three groups: RUTF-C, RUTF-L and A-HPF.

The primary outcome was recovery (defined as $WHZ \geq -2$ SD of the WHO standards and absence of oedema of feet) by 16 weeks after enrolment.²³ Secondary outcomes included weight gain, time to recovery, prevalence of diarrhoea, acute lower respiratory tract infection (ALRI) and fever, mortality and hospitalisations during the treatment phase (until recovery or 16 weeks after enrolment, whichever was earlier). Another secondary outcome was the proportion of children with $WHZ \geq -2$ SD at the end of the sustenance phase (16 weeks after completion of the treatment phase). The cost of the feeding regimens, the families’ and health workers’ perceptions about the regimens, and the factors that affect recovery (other secondary outcomes) will be published in separate manuscripts.

Study sites

We conducted the study in three diverse geographical settings in India—Rajasthan, Tamil Nadu and Delhi. The study populations were low-income households quite diverse, with a mix of rural and urban areas. The three sites also varied in the programmatic context. Enrolment began in October 2012 and follow-up was completed in April 2015.

Study oversight

The study was approved by the Government of India and the state governments. Oversight was provided by the National Research Alliance for SAM established by the Indian Government. An independent Data Safety Monitoring Board (DSMB) periodically reviewed the study and provided recommendations.

DSMB recommendations

In the original proposal, the period of treatment and measurement of the primary outcome were set at 8 weeks. This choice was based on the findings of studies in Africa that showed that most children with SAM recovered within 8 weeks of starting RUTF.^{12 24 25} Based on a *a priori* decision, the DSMB reviewed the study after the initial 20 enrolments. They recommended that the intervention be given for a maximum of 16 weeks, instead of the 8 weeks described in the initial protocol. The justification was that although recovery rates by 8 weeks were low, the intervention, if effective over a period of 16 weeks, would still be of considerable public health interest.

Additional suggestions were recommended during a DSMB review conducted when about 40% children had been enrolled. These included increasing the sample size and strengthening the support for feeding as recovery rates among enrolled children were still low. In response, peer supporters who would help caregivers to

feed their children were identified at all sites and the sample size was increased.

Sample size

The study involved two comparisons: between RUTF-C and A-HPF, and between RUTF-L and A-HPF. A-HPF was the comparison group. When we planned this study, published non-randomised studies conducted in Africa had shown 17–23% difference in recovery between RUTF and a standard diet.^{12 15 26} We therefore hypothesised a conservative 15% difference between the RUTF and the comparison group (A-HPF) for calculation of sample size. Assuming an 80% recovery in the intervention group and 65% in the comparison group (ie, a 15% difference) with 90% power and $\alpha=0.025$, we required 231 children in each group. We increased it by 10% to account for loss of follow-up resulting in the original sample size estimate of 765. When the overall recovery rate was observed to be lower than assumed, the DSMB recommended an increase in sample size to at least 900 children to preserve the power to test the a priori hypothesis of 15% difference between the intervention and comparison groups.

Study procedures

Identification of children with SAM

We conducted a door-to-door survey in the defined study populations to identify all children aged 6–59 months. After written informed consent from the caregiver, the mid-upper arm circumference (MUAC) was measured (Chasmors CTM03 tape; accuracy 1 mm). Children with MUAC<130 mm were brought to the study clinic. At the clinic, weight (Seca 385 digital weighing scale; accuracy 20 g) and height/length (Seca 417 infantometer for length, Seca 213 stadiometer for height; accuracy 1 mm) were measured, and oedema of feet checked. The WHZ were calculated using the WHO Growth Standards.²⁷ The WHO Anthro software was used for calculating WHZ (<http://www.who.int/childgrowth/software/en/>). Children with WHZ<-3 SD or oedema of feet, or both were identified as SAM.^{17 23} Children with complications were followed up and considered for enrolment after improvement.

Screening and enrolment

Physicians screened all children with SAM for signs of severe illness based on the Integrated Management of Neonatal and Childhood Illness (IMNCI) algorithms.²⁸ Haemoglobin was estimated (HemoCue method) and appetite tested using RUTF-C as the test feed. Children with severe illness requiring hospitalisation, allergy to milk and haemoglobin <6 g/dL, and who were unable to consume the test feed were considered to have complicated SAM and were taken to health facilities for hospital management. The remaining children with uncomplicated SAM, whose families were likely to remain in the study area over the next 4 months, and whose parents gave written informed consent were

enrolled. Children with a sibling previously enrolled in the study were excluded. MUAC, triceps and subscapular skinfold thickness (Holtain skinfold callipers; accuracy 0.2 mm) of enrolled children, and weight and height of mothers were also measured.

Allocation and concealment

A WHO statistician, not otherwise involved with the study, prepared randomisation lists. Randomisation was stratified by site and age categories (6–17 and 18–59 months) using block sizes of variable length (3, 6 or 9). Allocation into study groups was concealed using Serially Numbered Opaque Sealed Envelopes (SNOSE) prepared by the WHO. The allocation ratio was 1:1:1 and the children were recruited in all three groups according to the randomisation list. The SNOSE next in sequence was opened only after completing an enrolment.

Interventions during treatment phase

We delivered foods free of cost in the three study groups, with the aim of ensuring an intake of at least 175 kcal/kg body weight/day.

The composition of RUTF-C, packaged in 92 g sachets (Compact India, Gurgaon, India), conformed to the WHO recommendations.¹⁷ Each site team was trained in the preparation of RUTF-L by a consultant who had participated in the African studies. The preparation was carried out under stringent conditions that included controlled temperature and humidity, restricted access to the preparation room, hygienic conditions, periodic pest control and good ingredient quality. RUTF-L was prepared in a designated room by trained staff and packaged in transparent food grade 250 g jars.²⁹ The composition of RUTF-L was similar to the one used in African research studies and programmes, and conformed to the WHO recommendations (table 1).

Microbiological testing of RUTF-L was performed every 3 months. Samples were sent to an external accredited laboratory and tested for aflatoxin content, *Escherichia coli*, coliform count, yeast, moulds, pathogenic *Staphylococci*, *Salmonella*, *Listeria monocytogenes*, *Enterobacter* and *Clostridium perfringens*.

Families of children in the comparison group (A-HPF) were given raw ingredients to prepare foods. These included locally available and acceptable cereals and pulses, sugar, oil, milk and eggs. Recipes for making energy-rich and nutrient-rich foods for children were promoted. A micronutrient preparation providing the recommended daily intake of vitamins and minerals for a child with SAM was given to caregivers, to be added to the cooked meal prior to feeding.²³ In the A-HPF group, we gave food ingredients in excess of requirements for the child given the expectation of some sharing within the family. In all the three groups, we aimed to achieve intakes of 175 kcal/kg body weight/day for the enrolled child.

Table 1 Composition and appearance of RUTF-C and RUTF-L

| Description | RUTF-C | RUTF-L |
|----------------------|--------------------|------------|
| Energy (kcal)/100 g | 543 | 528 |
| Nutrient content (g) | | |
| Proteins | 15 | 15 |
| Lipids | 34.8 | 33 |
| Carbohydrates | 43.5 | 46 |
| Ingredients | | |
| Peanut paste | 30% | 26% |
| Sugar | 29% | 27% |
| Milk solids | 20% | 25% |
| Vegetable oil | 18% | 20% |
| Mineral mix | Identical* | Identical* |
| Vitamin mix | Identical† | Identical† |
| Emulsifier | Yes | No |
| Antioxidant | Yes | No |
| Consistency | Thicker and sticky | Thinner |
| Texture | Smooth | Granular |

*Minerals per 100 g: calcium 400 mg, phosphorus 400 mg, potassium 1100 mg, magnesium 110 mg, sodium <290 mg, iron 10 mg, zinc 12 mg, copper 1.5 mg, iodine 100 µg, selenium 30 µg.
 †Vitamins per 100 g: vitamin A 0.9 mg, vitamin D₃ 18 µg, vitamin K 21 µg, vitamin E 27 µg, vitamin C 54 mg, vitamin B₁ 0.5 mg, vitamin B₂ 1.8 mg, vitamin B₆ 0.7 mg, vitamin B₁₂ 1.6 µg, niacin 5.8 mg, Ca-D pantothenate 3 mg, folic acid 225 µg, biotin 70 µg.
 RUTF-C, centrally produced ready-to-use therapeutic food; RUTF-L, locally prepared ready-to-use therapeutic food.

During the treatment phase, household visits were carried out by a study worker with similar educational qualifications to the government's Accredited Social Health Activist (ASHA) who are women from the communities trained as health educators and promoters by the government, and a key cadre in India's community health worker programme designed to improve maternal and child health. The visits were conducted weekly to counsel, resolve caregivers' queries and difficulties, to replenish supplies, and to collect empty RUTF-L jars and wrappers of RUTF-C packets.³⁰ The workers used site-specific counselling cards made in the local language. The cards included messages on how frequently, how much and how to feed, on continuing breast feeding, good hygiene and advice on family meals. A copy of the card was also given to the family. In the A-HPF group, local, culturally appropriate, energy-rich and nutrient-rich recipes were also printed on the cards. Information on recommended recipes is provided in the online supplementary file. Information on intake of RUTF-L and RUTF-C was recorded; the amounts of ingredients used weekly were documented for the A-HPF group. For calculation of food consumption, the used packets (RUTF-C) or jars (RUTF-L) were collected from each home during the weekly visit throughout the treatment phase. The total calories consumed were calculated by multiplying the number of calories in a

packet (500 kcal for RUTF-C) and jar (1328 kcal for RUTF-L) by the number of packets or jars consumed by the child. The calorie consumption in kcal/kg/day was calculated by dividing the total calories consumed by the number of days the child was available during the treatment phase and weight at enrolment. We did not collect consumption data for the comparison group given the greater difficulty in capturing valid information. The neighbourhood peer support workers recruited post-DSMB recommendations visited homes several times a day to help caregivers feed their children in all the three groups. They were given a daily financial incentive for this activity.

Cointerventions in the treatment and sustenance phases

Co-interventions were similar in the three groups. At enrolment, all children received oral amoxicillin for 5 days. Those aged 2 years or older were given antihelminthics (mebendazole) for 3 days. Children with anaemia (haemoglobin ≥ 6 to ≤ 11 g/dL) in the A-HPF group were given iron and folic acid. A mega dose of vitamin A was given to children with signs or symptoms of vitamin A deficiency. Immunisation was facilitated according to the National Immunisation Schedule. Sick children visiting the study clinics were treated following the IMNCI guidelines.²⁸

During follow-up, sick children attending the study clinic or referred by workers during home visits were treated by physicians, and those with severe illness were referred to hospitals.²⁸ Hospitalised children were treated according to local policy. Transport and treatment were provided free of cost. The intervention was restarted after families returned home.

After completion of the treatment phase, the study team facilitated linkages between the families and the government-run *anganwadi* centres, where supplementary food is provided under the Integrated Child Development Services (ICDS) scheme.³¹ This was carried out over the next 16 weeks (sustenance phase).

Outcome measurement

During the treatment phase, an independent outcome measurement team took weekly anthropometric measurements. This team was blinded as far as possible to the group to which the child was allocated. They measured weight, height, MUAC, skinfold thickness using equipment similar to that used at enrolment, and looked for oedema of feet. Weight-for-height was estimated using the weight and height measured on that day. Information on diarrhoea morbidity, ALRI, fever and hospitalisation was also ascertained.

During the treatment phase, children with no change or deterioration in WHZ at 4 weeks post-enrolment or deterioration in WHZ for 2 consecutive weeks were taken to a paediatrician for assessment. Children who did not recover by 16 weeks were evaluated in hospitals. All hospitalisations and deaths were reported within 3 days to the site ethics committee, the WHO

and the coordination unit that provided oversight to the study.

At the end of the sustenance phase, anthropometry data were obtained during a single visit and we asked about hospitalisations during the 16 weeks since the completion of the treatment phase, that is, the sustenance phase.

Quality assurance

All teams were extensively trained prior to study initiation and periodically thereafter. Anthropometric measurement protocols were based on the WHO recommendations; these included training in measurement techniques, periodic standardisation of teams and daily calibration of equipment.³² Two 'gold standards' (persons with several years of experience in measurement and trainers for the anthropometry team) conducted standardisation exercises at all sites every 3 months. Equipment was calibrated every day. Supervisors reviewed activities daily. Quality control visits were conducted by an independent team through directly supervised and independent revisits for at least 1% each of follow-up and outcome measurement visits.

Ethical approvals

The study was approved by the institutional ethics committees of each participating institution (Society for Applied Studies, New Delhi: SAS ERC/40/2012; Christian Medical College, Vellore: IRB-A13-19-09-2012; Action Research and Training for Health, Udaipur: ARTH IEC dated 14 January 2013) and the WHO Ethics Review Committee (Protocol ID RPC538). Written informed consent was obtained from caregivers for each different activity.

Patient involvement

The study was designed in response to a national consultation with public health researchers, clinicians, nutritionists and community leaders. The study questions and the interventions were defined during the consultation. Prior to study initiation, families in the study area were engaged by the team about effective ways of supporting mothers in home treatment with SAM for children without complications requiring hospitalisation. During the study, peer supporters from the neighbourhood supported and motivated mothers of enrolled children. Community leaders and families helped in identification of these persons. Mothers helped in the identification of ingredients and recipes to be promoted in the group of children receiving augmented home foods. The study team assisted in strengthening the families' relationship with existing nutrition services (ICDS scheme).³¹ A consultation was held in partnership with the national government to disseminate findings and discuss the way forward. This resulted in several states in India launching a programme for home treatment of children with uncomplicated SAM. The team provided guidance in programme design.

Statistical analysis

Data from all sites were pooled and analysed using Stata software (V.12.0). Simple comparison of means and proportions was used to check comparability between groups. In the primary analysis, we made an overall comparison of outcomes between different groups. Analysis was conducted according to intention-to-treat. All children who completed the treatment phase and for whom outcome was known were included in the analysis. We used generalised linear models to compare the efficacy of the three regimens. We adjusted for baseline characteristics where there were small non-significant differences—maternal education, caste, religion, and family structure and also for enrolment age, sex, site, peer support and the pre-enrolment WHZ.

Two-sided tests were applied. For time to recovery, Kaplan-Meier plots were prepared and a Cox proportional hazard model was run. For these analyses, all enrolled children were included until they were in the study, that is, until recovery, completion of the 16 weeks treatment phase or until they were lost to follow-up.

In addition to the primary and secondary outcomes included in the protocol, additional analyses were planned prior to completing data collection. These included comparison of anthropometric status at enrolment and at the end of the study across the groups as well as the proportion of children with SAM at the end of the sustenance phase.

Definitions used

Diarrhoea was defined as passage of three or more loose or watery stools in a 24-hour period.

ALRI was defined as presence of cough or difficult breathing and either fast breathing or lower chest indrawing.

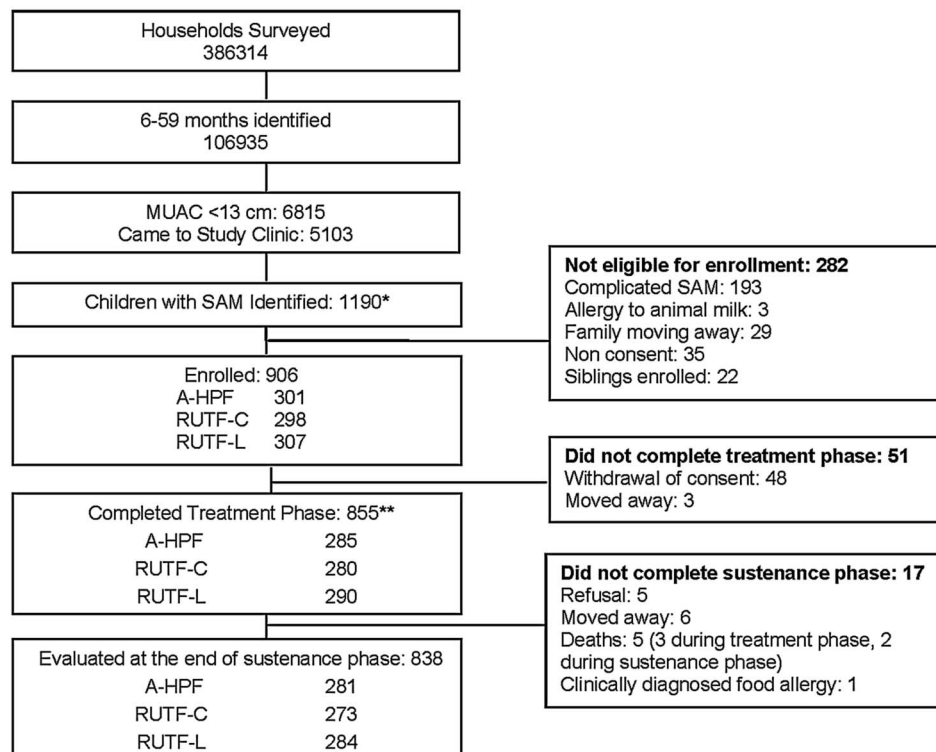
Fever was documented based on the caregiver's report.

RESULTS

From October 2012 to September 2014, 106935 children aged 6–59 months were identified through surveys at the three sites. The 6815 (6.4%) children who had MUAC<130 mm were referred to the study clinics. Of the 5103 (74.9%) who came to the study clinic, 1190 (23%) had SAM (WHZ<-3; [figure 1](#)). Two hundred and ninety-two (24.5%) children had a medical complication requiring referral to a hospital. They were revisited for about a month to ascertain resolution of complications; 98 of the children referred to hospital were enrolled after they recovered from the illness and were available at home. Nine hundred and six children with uncomplicated SAM were enrolled into the study ([figure 1](#)).

Eight hundred and fifty-five (94.4%) children completed the treatment phase and 838 (92.5%) children were measured at study completion or at the end of the sustenance phase.

Figure 1 Trial profile. A-HPF, micronutrient-enriched (augmented) energy-dense home-prepared foods; MUAC, mid-upper arm circumference; RUTF-C, centrally produced ready-to-use therapeutic food; RUTF-L, locally prepared ready-to-use therapeutic food; SAM, severe acute malnutrition.



*2 children were initially incorrectly identified as SAM but not enrolled

**3 children died in the treatment phase but were included as "not recovered" in the primary analysis

At enrolment, three-fourths of the children were stunted, 48% severely so (table 2). Only two children had oedema of feet. Almost half of the mothers had a body mass index under 18.5 (table 2).

While baseline characteristics were similar across the three groups, there were some important differences in family structure, maternal education, religion and caste.

The recovery rates with A-HPF, RUTF-C and RUTF-L were 42.8%, 47.5% and 56.9%, respectively (table 3). Children in the RUTF-L group had a significantly higher rate of recovery as compared with A-HPF (adjusted OR 1.71 (95% CI 1.20 to 2.43; $p=0.003$)). The recovery rates in the RUTF-C group compared with the A-HPF group were OR 1.28 (95% CI 0.90 to 1.82; $p=0.164$). The Cox proportional hazard model showed similar results. Adjusted HR compared with A-HPF group was 1.43 (95% CI 1.13 to 1.81, $p=0.003$) for RUTF-L and 1.22 (95% CI 0.95 to 1.56, $p=0.112$) for RUTF-C.

Among children who recovered by 16 weeks, time to recovery was significantly shorter both in the RUTF-C (adjusted difference -1.34 weeks, 95% CI -2.36 to -0.31 ; $p=0.011$) and RUTF-L (adjusted difference -1.17 weeks, 95% CI -2.16 to -0.17 ; $p=0.021$) groups compared with the A-HPF group.

The mean (SD) weight gain (g/kg/day) in the A-HPF, RUTF-C and RUTF-L groups was 2.64 (3.47), 3.05 (3.41) and 3.52 (3.92), respectively.

Diarrhoea, ALRI or fever was reported by families of 520 (71.5%) children. Eighty-two (9.6%) children were

hospitalised during the treatment phase. The proportion of children who were hospitalised or had diarrhoea, ALRI or fever was not significantly different across the three groups.

Recovery rates at 8 weeks after treatment are also presented as this was the original primary outcome. These were 26.6%, 34.8% and 40.7% in the A-HPF, RUTF-C and RUTF-L groups, respectively. The adjusted OR for the RUTF-L group compared with the A-HPF group was 1.83, 95% CI 1.27 to 2.64 ($p=0.001$) and 1.56, 95% CI 1.07 to 2.26 ($p=0.020$) for the RUTF-C group when compared with the A-HPF group.

The overall recovery rates in children whose families were offered peer support were substantially higher than in those who did not receive this support (55% vs 42%, $p<0.001$).

Kaplan-Meier curves showed that recovery started earlier in the RUTF-L group and the difference was maintained throughout the treatment phase (figure 2).

Sixteen weeks after completion of the treatment phase (sustenance phase), 838 children (92.5%) were available for follow-up (table 4). Of these, 123 (14.7%) met the definition of recovery, 402 (48.0%) met the definition of moderate acute malnutrition ($WHZ<-2$ and ≥-3) and 313 children (37.4%) had SAM (table 4). The proportion of children with SAM was significantly lower in the RUTF-L group (adjusted OR 0.58 (95% CI 0.40 to 0.85; $p=0.005$); correspondingly, those with moderate malnutrition were significantly higher (1.46, 95% CI 1.02 to 2.08; $p=0.039$) compared with the A-HPF group. The

Table 2 Baseline characteristics of enrolled children and their families

| | Treatment groups | | |
|--|------------------|----------------|----------------|
| | A-HPF (n=301) | RUTF-C (n=298) | RUTF-L (n=307) |
| Age at enrolment, mean (SD) | 25.7 (14.1) | 24.7 (13.9) | 25.7 (14.0) |
| Males | 166 (55.2) | 181 (60.7) | 178 (58.0) |
| Weight-for-height Z-score, mean (SD) | -3.5 (0.5) | -3.5 (0.4) | -3.4 (0.4) |
| <-3 to ≥-4 | 266 (88.4) | 267 (89.6) | 282 (91.9) |
| <-4 | 35 (11.6) | 31 (10.4) | 25 (8.1) |
| Height-for-age Z-score: mean (SD) | -3.0 (1.3) | -2.9 (1.2) | -3.1 (1.4) |
| ≥-2 | 75 (24.9) | 68 (22.8) | 67 (21.8) |
| <-2 to ≥3 | 83 (27.6) | 94 (31.5) | 87 (28.3) |
| <-3 to ≥-4 | 84 (27.9) | 82 (27.5) | 90 (29.3) |
| <-4 | 59 (19.6) | 54 (18.1) | 63 (20.5) |
| Mid-upper arm circumference: mean (SD) (cm) | 11.8 (0.8) | 11.8 (0.8) | 11.8 (0.8) |
| <11.5 | 76 (25.3) | 72 (24.2) | 76 (24.8) |
| 11.5 to 12.4 | 164 (54.5) | 163 (54.7) | 159 (51.8) |
| 12.5 to 13.0 | 61 (20.3) | 63 (21.1) | 72 (23.5) |
| Fever/diarrhoea/cough or fast breathing) in previous 2 weeks | 159 (52.8) | 162 (54.4) | 166 (54.1) |
| Mother's age, mean (SD) | 27.1 (5.6) | 27.7 (5.8) | 27.4 (4.9) |
| Mother's BMI<18.5 kg/m ² * | 134 (47.9) | 135 (48.0) | 151 (51.7) |
| Mother never been to school | 117 (38.9) | 116 (38.9) | 136 (44.3) |
| Mother's years of schooling, median (IQR) | 5 (0-9) | 5 (0-10) | 5 (0-8) |
| Father never been to school | 59 (19.6) | 66 (22.1) | 69 (22.5) |
| Father's years of schooling, median (IQR) | 7 (3-10) | 8 (3-10) | 7 (2-10) |
| Religion of head of family | | | |
| Hindu | 242 (80.4) | 246 (82.6) | 248 (80.9) |
| Muslim | 54 (17.9) | 44 (14.8) | 39 (12.7) |
| Other | 5 (1.7) | 8 (2.7) | 20 (6.5) |
| Caste (social class) of head of family | | | |
| Schedule caste/schedule tribe (most disadvantaged) | 141 (46.8) | 134 (45.0) | 158 (51.5) |
| Other backward class (intermediate) | 101 (33.6) | 104 (34.9) | 86 (28.0) |
| Other caste (higher class) | 59 (19.3) | 60 (19.9) | 63 (19.7) |
| Persons residing in the house, mean (SD) | 5.9 (2.4) | 5.7 (2.5) | 5.9 (2.4) |
| Piped water | 55 (18.3) | 51 (17.1) | 57 (18.6) |
| Flush toilet within the house | 145 (48.2) | 150 (50.3) | 151 (49.2) |
| Facility delivery | 204 (67.8) | 222 (74.5) | 204 (66.4) |
| Family with below poverty line card | 97 (32.2) | 100 (33.6) | 105 (34.2) |
| Family structure, nuclear† | 175 (58.1) | 196 (65.8) | 189 (61.6) |

All values are n (%) unless otherwise indicated.

*BMI values not available for 53 mothers: A-HPF (n=21), RUTF-C (n=17), RUTF-L (n=15).

†Pair of adults living with their children.

A-HPF, micronutrient-enriched (augmented) energy-dense home-prepared foods; BMI, body mass index; RUTF-C, centrally produced ready-to-use therapeutic food; RUTF-L, locally prepared ready-to-use therapeutic food.

WHZ between enrolment and the end of the sustenance phase improved for all enrolled children. However, the improvement appears to be greater in the RUTF-L group compared with the A-HPF group (difference in mean Z-scores 0.11, 95% CI 0.0 to 0.22, $p=0.051$; [table 4](#)). The mean (SD) amount of RUTF-L consumed was 193.27 (94.03) g/day and RUTF-C 172.83 (89.10). The mean (SD) kcal/kg/day consumed was 140.19 (65.41)

and 129.69 (65.09), respectively. Consumption was not measured in the A-HPF group.

DISCUSSION

This is the first randomised trial evaluating RUTFs with energy-rich and nutrient-rich home foods for the management of children with SAM without complications.

Table 3 Primary and secondary outcomes in the treatment phase

| | Treatment groups | | | Adjusted OR* 95% CI p Value between | |
|--|------------------|------------------|------------------|--|-----------------------------------|
| | A-HPF n=285 | RUTF-C n=280 | RUTF-L n=290 | RUTF-C and A-HPF | RUTF-L and A-HPF |
| Primary outcome | | | | | |
| Recovered by 16 weeks | 122 (42.8) | 133 (47.5) | 165 (56.9) | 1.28 (0.90 to 1.82) p=0.164 | 1.71 (1.20 to 2.43) p=0.003 |
| Secondary outcomes | | | | | |
| Weight gain in g/kg/day of baseline weight | | | | Adjusted difference | |
| Mean (SD) | 2.64 (3.47) | 3.05 (3.41) | 3.52 (3.92) | 0.44 (−0.16 to 1.02) p=0.148 | 0.89 (0.30 to 1.48) p=0.003 |
| Median (IQR) | 1.30 (0.80–3.02) | 1.61 (0.86–4.03) | 1.96 (0.93–4.77) | | |
| Time to recovery (week) in children who recovered during the treatment phase | | | | | |
| Mean (SD) | 7.12 (4.54) | 5.91 (4.03) | 6.05 (4.00) | −1.34 (−2.36 to −0.31) p=0.011 | −1.17 (−2.16 to −0.17) p=0.021 |
| Median (IQR) | 6 (3–10) | 5 (3–8) | 5 (3–9) | | |
| Children died | 0 | 2 | 1 | | |
| | | | | Adjusted OR* 95% CI | |
| Children hospitalised | 30 (10.5) | 30 (10.7) | 22 (7.6) | 0.96 (0.55 to 1.67) p=0.884 | 0.72 (0.40 to 1.31) p=0.286 |
| | n=243 | n=235 | n=249 | | |
| Children with diarrhoea† at any time during the treatment phase | 101 (41.6) | 92 (39.2) | 109 (43.8) | 0.94 (0.62 to 1.42) p=0.773 | 1.19 (0.79 to 1.78) p=0.413 |
| Children with ALRI‡ at any time during the treatment phase | 38 (15.6) | 24 (10.2) | 35 (14.1) | 0.59 (0.34 to 1.04) p=0.069 | 0.84 (0.50 to 1.41) p=0.506 |
| Children with fever§ at any time during the treatment phase | 162 (66.7) | 142 (60.4) | 144 (57.8) | 0.74 (0.50 to 1.11) p=0.151 | 0.69 (0.46 to 1.02) p=0.062 |

All values are n (%) unless otherwise indicated.

*Generalised Linear Model (GLM) model sex, WHZ at enrolment, family structure, age at enrolment, maternal education, religion, caste, site and peer support.

†Diarrhoea: passage of ≥ 3 loose or watery stools in a 24-hour period.

‡ALRI: presence of cough or difficult breathing and either fast breathing or lower chest indrawing.

§Fever as reported by caregiver.

A-HPF, micronutrient-enriched (augmented) energy-dense home-prepared foods; ALRI, acute lower respiratory tract infection; RUTF-C, centrally produced ready-to-use therapeutic food; RUTF-L, locally prepared ready-to-use therapeutic food; WHZ, weight-for-height Z-score.

Our main finding is that in an efficacy study, locally produced RUTF is superior to A-HPF in achieving recovery. Our study confirms the findings of quasi-randomised trials in Malawi on the efficacy of RUTF compared with standard diets for home management of children with uncomplicated SAM.^{12 15 25}

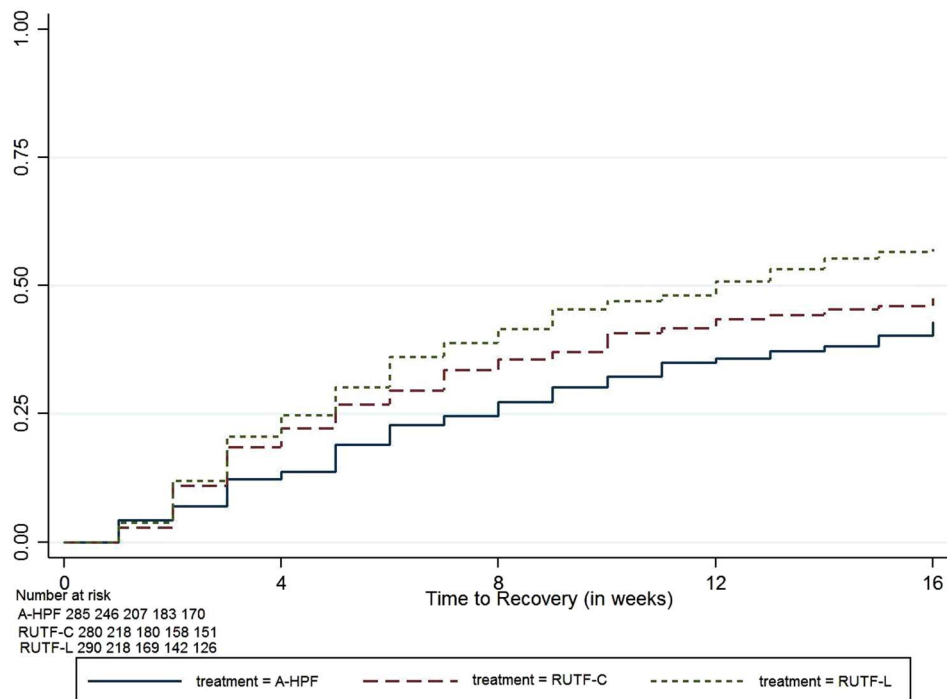
In this trial, about half the children recovered with a package of interventions that included diets of high nutritional value provided free of cost, peer support for feeding, antibiotics at the initiation of treatment and increased access to healthcare for morbidity.

Comparison with other studies and interpretation

The recovery rates are lower than those observed in Africa, despite a longer duration of treatment and support to families for feeding. One of the reasons for

the lower recovery rates may be that almost all children in our study had marasmus. In similar studies in Africa, the majority of children had kwashiorkor, and those with kwashiorkor had higher recovery rates compared with those with marasmus.^{24 25 33} The prevalence of oedema in children with SAM in African studies ranged from 39% to 80% but was only 0.2% in our trial. The mean WHZ was also lower in our study compared with the African studies (detailed information in online supplementary file).^{12 15 24 26} The evidence suggests that children with kwashiorkor tend to have higher weight-for-age than those with marasmus and may need to gain less weight to recover once they no longer have oedema. Diarrhoea impairs weight and height gain and thus leads to lower recovery rates.^{34 35} Infection also causes malnutrition due to deterioration of immune

Figure 2 Time to recovery in the three treatment groups. A-HPF, micronutrient-enriched (augmented) energy-dense home-prepared foods; RUTF-C, centrally produced ready-to-use therapeutic food; RUTF-L, locally prepared ready-to-use therapeutic food.



function which increases susceptibility to infection and metabolic responses that impair nutritional status.³⁶ Further, around half the mothers of enrolled children were themselves malnourished; this may have resulted in less energetic efforts at feeding their malnourished children. Maternal underweight is one of the risk factors for childhood malnutrition and is closely associated with fetal, child and adolescent undernutrition.³⁷

An additional explanation for the differences is that most African studies used height at enrolment to calculate WHZ during the follow-up period. We instead used subsequent height, measured concurrently with weights. In our study, height and weight were measured together every week during the follow-up period. Using height at enrolment increases the proportion of children who reach the cut-off for recovery.

The average weight gain in our trial was 3.5 g/kg/day. This was considerably lower than 9.4 g/kg/day observed in a study in Central India but closer to the observed in a community-based management of SAM project in Bihar that reported a weight gain of 4.9 g/kg/day, possibly overestimated due to exclusion of defaulters (38%).^{38 39} In another trial from North India, the recovery rate (defined as gaining 115% of baseline weight) was 46% and the weight gain was 3 g/kg/day, both similar to our study.⁴⁰

Important lessons were gained from study implementation. The most valuable lesson was that in addition to the type of diet, extra support for feeding seems important in our setting for weight gain and recovery. Help from local experienced women seemed to improve food intake. It is likely that peer supporters, in addition to practical help, enhanced engagement and skills of the mother, resulting in children eating more.^{41 42}

The finding that many children remain or slide back into moderate or severe malnutrition as early as within 16 weeks after the end of treatment is important for programmes. It underscores the importance of adequately sustained nutrition support after RUTF treatment is stopped. While linkages between families and the government *anganwadi* centres that provide supplementary nutrition services were established, additional measures may be required to sustain the improvements from the treatment phase. These may include close monitoring, improved counselling, support to caregivers, provision of additional food supplements, including giving RUTF for a longer period, and prompt treatment of illnesses. A recent trial in moderately malnourished Malawian children found that those treated with supplementary foods for 12 weeks had lower relapse rates and remained well nourished during the subsequent follow-up period of 12 months.⁴³ Such longer period of care is more likely to be feasible in settings where management of children with SAM is embedded within efforts to prevent malnutrition.

Strengths and weaknesses of the study

Our study was a multicentre randomised trial conducted in different regions of India covering diverse populations. The community-based identification of SAM contributed to greater generalisability. Rigorous supervision and control of intervention delivery ensured uninterrupted food supplies across all the groups. Sharing of ingredients for preparation of foods at home is unlikely to have significantly reduced the amount of food offered to the child with SAM because supplies were provided in excess of the child's consumption and in-depth interviews with caregivers revealed little evidence of sharing.

Table 4 Secondary outcomes during the sustenance phase (16 weeks after the end of the treatment phase)

| | A-HPF n=281* | RUTF-C n=273† | RUTF-L n=284‡ | Adjusted OR 95% CI p Value between§ | |
|---|----------------------------|------------------|------------------|--|----------------------------------|
| | | | | RUTF-C and A-HPF | RUTF-L and A-HPF |
| At the end of the sustenance phase | | | | | |
| WHZ \geq -2 (met definition of 'recovery') | 41 (14.6) | 33 (12.1) | 49 (17.3) | 0.78 (0.47 to 1.34) p=0.392 | 1.12 (0.74 to 1.95) p=0.464 |
| WHZ <-2 to \geq -3 (moderate acute malnutrition) | 121 (43.1) | 129 (47.3) | 152 (53.5) | 1.26 (0.88 to 1.81) p=0.199 | 1.46 (1.02 to 2.08) p=0.039 |
| WHZ <-3 (severe acute malnutrition) | 119 (42.4) | 111 (40.7) | 83 (29.2) | 0.87 (0.61 to 1.26) p=0.470 | 0.58 (0.40 to 0.85) p=0.005 |
| Change between enrolment and the end of the sustenance phase | | | | | |
| | Adjusted difference 95% CI | | | | |
| WHZ, mean (SD) | 0.65 (0.70) | 0.65 (0.76) | 0.74 (0.76) | -0.01 (-0.12 to 0.11) p=0.906 | 0.11 (-0.00 to 0.22) p=0.051 |
| Height-for-age Z-score, mean (SD) | 0.08 (0.47) | 0.04 (0.65) | 0.07 (0.50) | -0.03 (-0.12 to 0.06) p=0.437 | -0.00 (-0.09 to 0.08) p=0.971 |
| Mid-upper arm circumference, mean (SD) | 0.75 (0.68) | 0.68 (0.72) | 0.81 (0.75) | -0.06 (-0.17 to 0.04) p=0.226 | 0.08 (-0.02 to 0.19) p=0.115 |

Three children (two in the RUTF-C group and one in the RUTF-L group) died during the treatment phase and two children (one each in the RUTF-C and RUTF-L groups) died during the sustenance phase. All values are n (%) unless otherwise indicated.

*Of the 301 enrolled children, 285 completed the treatment phase and of them 281 completed the sustenance phase. Reasons for loss: refusal (n=3), moved away (n=1).

†Of the 298 enrolled children, 280 completed the treatment phase and of them 273 completed the sustenance phase. Reasons for loss: moved away (n=3), clinically diagnosed allergy (n=1), died during the treatment phase (n=2) and died during the sustenance phase (n=1).

‡Of the 307 enrolled children, 290 infants completed the treatment phase and of them 284 completed the sustenance phase. Reasons for loss: refusal (n=2), moved away (n=2), died during the treatment phase (n=1) and died during the sustenance phase (n=1).

§GLM model adjusted for all potential covariates as sex, WHZ at enrolment, family structure, age at enrolment, maternal education, religion, caste, site and peer support.

A-HPF, micronutrient-enriched (augmented) energy-dense home-prepared foods; RUTF-C, centrally produced ready-to-use therapeutic food; RUTF-L, locally prepared ready-to-use therapeutic food; WHZ, weight-for-height Z-score.

The outcome measurement team was independent from the intervention delivery team and workers underwent periodic standardisation exercises to ensure quality of anthropometric data.

Our study results also make an additional contribution to the literature because in the past children with SAM have been treated for 8 weeks. Continuing treatment for 16 weeks provides added value in this context where recovery rates were lower than expected at 8 weeks.

The study had some limitations. Around 25% of the children with MUAC<13 cm did not come to the study clinic. This might have affected generalisability. This, however, should not have affected the internal validity as children were only randomised after the confirmation of measurements at the clinic. Blinding could have further reduced the risk of bias but this was not feasible as the three interventions had visibly different characteristics—one was provided in packets, the other in jars and the third comprised of food ingredients. Based on findings from the initial months, counselling was intensified in all three groups through peer supporters. Therefore, children enrolled earlier received less intensive counselling and help than those enrolled later in the trial. The overall recovery rates we reported are therefore likely to be conservative. We lacked a reliable measure for consumption in the group given ingredients to prepare food

at home (A-HPF) due to the complexity of obtaining valid quantitative recalls for the recipes actually used.

Over 40% of children did not recover after RUTF use for 16 weeks. Since the therapeutic foods were discontinued as soon as the child met the definition of recovery, even a small deterioration in WHZ would mean that the child no longer met the definition for recovery by the time of the measurement 16 weeks later.

Implications

Our study shows that home-based management of children with uncomplicated SAM is an effective and feasible option and that use of a RUTF-L results in higher recovery rates than feeding nutrient-dense and calorie-dense home foods. The gains observed during the initial 16 weeks, however, decline after treatment. Other approaches need to be considered to improve long-term outcomes including prolonged use of a RUTF-L. Setting up local units for production of RUTF does not require huge investment in terms of equipment, infrastructure or personnel. The procedures for production are systematic and simple to replicate.

Despite the effectiveness of home-based management, additional or alternative approaches are needed for the relatively large proportion of children with

uncomplicated SAM who do not recover after treatment for 16 weeks.

Our findings indicate that rethinking about ways to combat the problem of severe malnutrition in children are required.

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Contributors All authors contributed substantially to the design and undertaking of the study, its analyses and writing of the manuscript. NB, SBM, AB, SDI, JM and RB designed the study. NB and ST coordinated the study and did data management and analysis, with technical support from RB, JM and SY. The following were responsible for the day-to-day implementation: SBM, SM and HSS (Delhi); AB, RAP and VRM (Vellore); and SDI, KI and VS (Udaipur). The study results were interpreted and the manuscript was prepared jointly during a workshop and has the final approval of all authors. NB affirms that the manuscript is an honest, accurate and transparent account of the study; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Efficacy of three feeding regimens for home-based management of children with uncomplicated severe acute malnutrition: a randomised trial in India

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