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Randomized, Double-Blind Controlled Clinical Effectiveness Trial Comparing a Novel 10% Milk Ready-to-Use Therapeutic Food with the Standard 25% Milk Ready-to-Use Therapeutic Food in the Treatment of Severe Acute Malnutrition in Rural Malawian Children

Mark J. Manary, Heidi L. Sandige and Kenneth Maleta

December 2009

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Abstract

Severe childhood malnutrition is defined as having a weight for height Z-score (WHZ) < -3 or bilateral pitting oedema. Standard therapy for cases of severe acute malnutrition without complications is home-based therapy with milk-peanut based RUTF. The cost of ingredients in RUTF limits its availability in resource-poor countries, with powdered milk constituting 67 percent of the cost. In this clinical effectiveness trial, severely malnourished children were given either a reduced milk formulation of RUTF (10 percent milk) in which milk was replaced with soy protein, or the standard formulation of RUTF (25 percent milk). Children received isocaloric quantities of the foods (733 kJ/kg/d) for up to eight weeks with biweekly follow up. The primary outcome was recovery, defined as having a WHZ of -2 and no oedema. A total of 1874 children were enrolled in the study. Children receiving 10 percent milk had a lower rate of recovery compared to those receiving the standard therapy (84 percent in the 25 percent milk group and 81 percent in the 10 percent milk group). Nonlinear regression modeling showed type of food to be a statistically significant term in rate of recovery. Overall, children who received the 10 percent milk formulation had slower rates of weight gain and slower MUAC gain. Differences of gain in stature were not statistically significant. Treating severely malnourished children with a 10 percent milk RUTF results in a lower rate of recovery and slower growth rates when compared to the standard 25 percent milk RUTF.

Introduction

Over the past nine years, fortified ready-to-use foods have made a remarkable impact on the treatment of malnutrition in children in sub-Saharan Africa. These lipid paste foods resist bacterial contamination because they contain very little water, do not require cooking and are very energy dense (5.5 kcal/g) (Manary 2006). These characteristics make them ideally suited for use in places in which food insecurity is common and hygiene is poor.

Ready-to-use therapeutic food (RUTF) refers to a lipid paste with a formulation that meets the compositional requirements for the treatment of severe malnutrition (composition is equivalent to F-100) as set forth by the World Health Organization (WHO). The only efficacy trial conducted with RUTF was in Senegal in 2001, in which 70 children were fed either F-100, a standard milk-based food, or RUTF. In this trial, there were no adverse events, and the rate of weight gain among those children taking RUTF was 1.5 fold greater than children receiving F-100 (Diop et al. 2003).

The first effectiveness trial with RUTF, conducted in 2001, used home-based therapy with RUTF to treat severely malnourished children. This trial compared three home diets: RUTF, corn/soy blend, and a peanut fortified spread. This trial demonstrated that the complete RUTF diet was associated with the best outcome; 95 percent of children recovered (Manary 2004). RUTF allows for treatment in the home, a reversal of former practices in which children were treated as inpatients and only 25 percent of children recovered (Brewster 1997). Home-based therapy offers the advantages of being more hygienic because the alternative, inpatient care, is often delivered in overcrowded facilities where communicable disease is common. Hospitalization requires that an adult stay with the child for the duration, and consequently pulls mothers, mostly subsistence farmers, away from families and fields, often with deleterious results to the family's food production. RUTF made with local ingredients has been shown to achieve the same recovery rate as imported RUTF (Sandige 2004).

In 2003, a large, controlled clinical trial was conducted in which home-based therapy with RUTF was compared to standard inpatient therapy (Ciliberto 2005). In this trial, RUTF achieved 79 percent recovery, while standard therapy was effective in only 46 percent of children. Since that time, RUTF has been used operationally in Malawi; one documentation of its operational use showed that recovery rate was 89 percent for severe childhood malnutrition (Linneman 2007). RUTF has been endorsed by the UN agencies, including the WHO, World Food Programme and UNICEF, as the most effective method to restore the health of severe/acute malnourished children (WHO 2007). Malawi instituted a national program for the treatment of severe malnutrition in 2007 that encompasses all districts; this program includes home-based therapy with RUTF as trialed through the College of Medicine.

RUTF contains 25 percent milk, an expensive ingredient that is not readily available worldwide. At current market prices, milk constitutes 67 percent of the ingredient cost of RUTF. While the inclusion of some source of animal protein such as milk is thought to be prudent (Schack-Nielsen 2007), such a large amount of milk seems unnecessary when standard human nutrient requirements are considered. Soy has been successfully substituted for animal products in a variety of other foods, including infant formula. Substituting soy for a portion of the milk in RUTF would reduce costs and increase availability. The purpose of this clinical trial was to determine conclusively whether soy might be substituted for a portion of the milk without a reduction in clinical efficacy. The hypothesis tested was that 25 percent milk RUTF would result in a superior recovery rate when compared to 10 percent milk RUTF.

Subjects and Methods

Study area. Fifteen rural study sites were identified in the southern region of Malawi based on census reports of severely malnourished children provided by the World Food Programme: Makhwila health center (Chikwawa), Mitondo health post (Chikwawa), Nkhate market village site (Chikwawa), Chiconde village site (Mulanje), Ntonya health post (Mulanje), M'biza health center (Mulanje), Chamba health center (Machinga), Mposa health center (Machinga), Machinga health center (Machinga), Nainunje health

center (Machinga), Mlomba health center (Machinga), Chikweo health center (Machinga), Ntaja health center (Machinga), Mayaka health center (Zomba), and Makhwapala health center (Zomba).

Subjects. Children aged 6-60 months present at sites from July 2008 to April 2009 were screened for eligibility. Children with severe malnutrition with no signs of systemic infection and with a good appetite were eligible for the study. Severe malnutrition was defined using a modified version of the WHO's current standards (weight-for-height Z-score (WHZ) < -3 or with bilateral pitting oedema and no signs of systemic infection), which incorporated a simplified reference chart combining male and female WHZ reference values. Children known to have chronic illness including HIV, cardiac disease, congenital abnormalities, cerebral palsy, cancer or those who had participated in a treatment program for severe malnutrition within the past 12 weeks were not eligible for the study. Informed consent was obtained from all participating caretakers. The study was approved by the College of Medicine Research and Ethics Committee, University of Malawi, and the Human Studies Committee of Washington University School of Medicine.

Enrollments were temporarily halted for four weeks in December 2009 to ensure continued availability of all ingredients needed for production of study foods, specifically the concentrated vitamin and mineral supplement. During this four-week period, all study subjects were maintained on continuous treatment and received the appropriate study formulation. All new children presenting for screening and treatment were given standard therapy, and were treated separately from the study population. Study enrollment resumed when the question of availability of ingredients was resolved.

Study design. This study was a randomized, clinical effectiveness trial of two locally produced foods for the treatment of severe malnutrition.

Children were randomly assigned to either 25 percent milk RUTF or 10 percent milk RUTF. Caretakers chose an envelope that contained one of six letters (A-F). Three of these letters corresponded to the 25 percent milk formulation and three to the 10 percent milk formulation. The letter was recorded separately from the child's clinical measurements. Field workers involved in the randomization process did not know which letter corresponded to which food. Field assistants who knew which letter corresponded to which food coordinated the food distribution process but did not assess the participants. Field workers and investigators remained unaware what type of food each child received for the duration of the study.

Children were assessed biweekly and participated in the study until they clinically recovered or after they had received four biweekly treatments without recovery. If the child remained wasted after four return visits or clinically worsened during treatment, the child was referred for medical evaluation and treatment. Worsening condition was defined as weight loss > 400 g, increasing severity of edema or anorexia.

The primary outcome was recovery, defined as simultaneously having no oedema and a WHZ of at least -2. Secondary outcomes included the rates of gain in weight, stature and mid-upper arm circumference (MUAC), and the development of adverse outcomes such as death or clinical deterioration of the subject's condition such as anorexia, worsening oedema, significant weight loss or evidence of systemic infection requiring inpatient admission.

The sample size was calculated to be 1800 children divided equally between the two foods. This sample size was chosen assuming that the standard recovery rate is 85 percent and using a one-sided difference of equivalence to detect a difference in recovery rates between the two foods of five percentage points with 95 percent sensitivity and 90 percent power. This method of determining the sample size was used, even though the intention was to analyze the outcomes using non-linear regression, because there are no accepted methods for determining sample size for non-linear regression analyses.

The trial was registered with Controlled Clinical Trials in the UK with the registration number of ISRCTN54186063, which can be accessed at http://www.controlled-trials.com/ISRCTN54186063.

Study participation. Caretakers brought their children for screening at which time each child was checked for oedema and had his/her weight, height and MUAC measured by trained study staff. Weight was

measured using an electronic scale (SECA model 334; precision 5 g). Length was measured in triplicate using a canvas measure mat and the mean value was used as the length (SECA model 210; precision 0.25 cm). MUAC was measured with a standard insertion tape (TALC). The scale was checked for accuracy with a known weight every two weeks and recalibrated if necessary. Upon enrollment, the caretaker of the participating child was interviewed to obtain basic demographic information, including the child's date of birth, sex, history of physical illness, and family background. Caretakers and children returned to the clinic for reassessment every two weeks. At each visit, the child was checked for oedema and measurement of the child's weight, length, and MUAC were taken. Children were checked for adverse reactions to the food such as development of rash or vomiting, and any reactions were noted.

Senior research nurses instructed caretakers on how much of the food to feed the enrolled study child each day. They emphasized that the food should not be shared with other members of the household and that the food should be treated as medical therapy for the affected child. They also emphasized that the food should serve as a replacement for other foods and should not be mixed or diluted in porridge. Caretakers were given a two-week supply of food for the enrolled child based on the child's weight. If the subject was a twin, an additional supply of food was given to the caretaker to ensure that the subject received a full ration and to limit sharing between the children. If there were two study subjects in the same household, both children were given the same kind of food to eliminate the possibility of confounding of study foods. If there was a moderately malnourished child and a study subject in the same household, the caretaker was instructed to treat both children as severely malnourished and the children were given the same kind of food to eliminate the possibility of confounding foods.

Food products. The two food products were 25 percent milk RUTF (26 percent peanut paste/25 percent dry skimmed milk) and a 10 percent milk RUTF (26 percent peanut paste/15 percent whole soy flour/10 percent dry skimmed milk). The remainder of the food was comprised of vegetable oil and sugar, added in palatable ratios. Concentrated minerals and vitamins were added to both types of RUTF from Nutriset (Malaunay, France). Children in both groups received rations of 733 kJ/kg/d. The quantity of food provided, determined by the child's body weight, was based on meeting the estimated energy requirement for catch-up growth in severely malnourished children. The cost of the food in Malawi at the time of the study for locally manufactured 25 percent milk RUTF was US$4.92/kg and US$3.80/kg for 10 percent milk RUTF.

The nutritional content of the two foods is shown in Table 1. A specially formulated micronutrient mixture was used for the 10 percent milk RUTF so that the micronutrient content in each of the two foods was similar. The foods were packaged in 245 g plastic jars and procured from Project Peanut Butter (Blantyre, Malawi). The food production facility is certified by the Malawi Bureau of Standards and produces these foods in accordance with the WHO Codex Alimentarius. The ingredients were available locally except for the micronutrient mix, which was imported from Nutriset.

Acceptability testing of the 10 percent milk RUTF was undertaken at five health centers in June 2008 by giving 30 g of the 10 percent milk RUTF to 150 well-nourished Malawian children aged 1-3 years. 137/150 consumed the test food entirely, and no child objected to the taste or texture. Vomiting was not observed during the test feeding exercises.

Data analysis. Summary enrollment characteristics were calculated as means ± SD for continuous measurements and as n (percentage) for dichotomous measures. Anthropometric indices were calculated using WHO 2009 standards (WHO 2009). The rate of weight gain was expressed as g/kg/d, which normalizes this rate to the initial body weight and the duration of treatment. Rates of length and MUAC gain were normalized to the duration of treatment.

To assess the effect of therapeutic food on recovery and growth, nonlinear regression modeling using time as an interacting covariate was used (SPSS 15.0 for Windows, Chicago, IL). While randomization made the groups equivalent at the onset, this analysis technique accounted for effects of several covariates through the course of the treatment period. The primary outcome was recovery. Secondary outcomes were weight gain, gain in stature and MUAC gain. Therapeutic food, age, sex, whether the child was a twin, whether the child's mother was alive, whether the child's father was alive, whether the child

had oedema, enrollment WHZ, enrollment height-for age Z-score (HAZ), the study site, the presence of fever, cough or diarrhea on enrollment and whether the child had previously been treated for malnutrition were assessed as covariates. The model did not include a time independent term representing the food group, since the groups were equivalent at the onset. A clustering term in the model was also included to account for pairs of twins both enrolled in the study and living in the same household. Intention to treat analysis was used. For each non-linear regression model, a r^2 value was calculated as 1- (Residual Sum of Squares)/(Corrected Sum of Squares). Coefficients in the regression models with 95 percent CI that did not include zero were considered to be statistically significant.

To compare children with poor outcomes, including death, to those that recovered, the enrollment characteristics of each group were tabulated and comparisons were made using Student's t-test for continuous parameters and using Fisher's Exact Test for dichotomous parameters. *P* values < 0.05 were considered to be significant.

To compare the case fatality rate in this study to international standards for the treatment of malnutrition, an estimate of the predicted case fatality rate was made using the method of Prudhon et al. and compared to the actual case fatality rate (Prudhon et al. 1997).

Results

A total of 1961 children were recruited into the study and 1874 children completed the study (Fig. 1; Table 2). The number of children enrolled at each site in each food group in shown in Table 3. A portion of twins were excluded from participation at five out of 15 sites because all twins at those sites were referred to a concurrent study. No caretakers refused enrollment and no participants experienced an adverse reaction to either the 25 percent milk formulation or the 10 percent milk formulation of RUTF. A total of 51 children (3 percent) were lost to follow up. Community field workers followed each case within one month of the child not returning, and reported in all cases that these caretakers had left the area in search of food or work and were untraceable. Only children without oedema were more likely to default ($P < 0.05$, Table 4).

At each follow-up visit, caretakers were asked whether the child was consuming the study food well, and whether the child was consuming almost all of the ration that was dispensed. Together, positive answers to these questions constituted an adequate intake. For the children who received 10 percent milk RUTF, 860/887 (97 percent) of their caretakers reported that they consumed an adequate intake after two weeks of participation, and 817/834 (98 percent) of their caretakers reported adequate intake after four weeks of participation. Among children receiving 25 percent milk RUTF, adequate intake was reported in 874/908 (96 percent) after two weeks of participation and in 850/866 (98 percent) after four weeks of participation. Differences after two and four weeks were not significantly different (Fisher's Exact Test, $P = 0.44$ and 0.86 respectively)

The outcomes of the children are shown in Table 5. The recovery rate among children receiving 25 percent milk RUTF was 84 percent and 81 percent among children receiving 10 percent milk RUTF ($P = 0.11$, Fisher's Exact Test).

Non-linear regression modeling of recovery found that the regression model had $r = 0.51$. The most important term in the model is, of course, the duration of treatment. Other terms that were associated with recovery with larger, statistically significant coefficients were whether the mother and father were alive, the degree of wasting, and whether the child received 25 percent milk RUTF (Table 6).

Overall, children who received the 10 percent milk formulation recovered more slowly when compared to children who received the 25 percent milk formulation (Figure 2) especially within the first two weeks. Children with kwashiorkor who received the 10 percent milk RUTF did not lose their oedema as quickly those who received the 25 percent milk RUTF. Recovery rates for marasmic children were nearly identical in both treatment groups.

The outcomes of the children with and without oedema are in Tables 7 and 8 respectively. The recovery rates for children with oedema receiving either 25 percent milk RUTF or 10 percent milk RUTF was 88 percent and 85 percent respectively (*P*=0.10, Fisher's Exact Test). There was little difference in the recovery rates of marasmic children receiving either 25 percent milk RUTF or 10 percent milk RUTF.

Fifty-nine children were referred for inpatient care during the course of therapy: 39 of these children in the 10 percent milk RUTF group and 20 in the 25 percent milk RUTF group (*P* = 0.01, Fisher's Exact Test). Table 9 describes the differences between the reasons for referral between these two groups. While more children who received 10 percent milk RUTF were referred for inpatient therapy, there is no distinctive pattern of signs and symptoms among these children.

Non-linear regression modeling was used to compare rates of growth between children receiving the two study foods. The terms in all models with the strongest association with greater growth was of course, the duration of treatment. For weight gain, the regression model had a r = 0.37. Other terms that were associated with weight gain with larger, statistically significant coefficients were a greater degree of wasting, female sex, younger age and whether the child received 25 percent milk RUTF (Table 6).

For MUAC gain, the model had an r = 0.40. A greater degree of wasting on enrollment was strongly associated with the rate of MUAC gain in this model (Table 6).

For height gain, the model had a r = 0.26, and the lowest among the regression models. Other terms that were associated with height gain with larger, statistically significant coefficients were whether the child was a twin and receiving 25 percent milk RUTF (Table 6).

Figures 3, 4 and 5 illustrated the differences in weight gain between the children receiving the 25 percent milk RUTF and the 10 percent milk RUTF.

Children who did not recover were more likely to have lower MUAC, WHZ and HAZ. They were less likely to have their mothers and fathers alive, less likely to have kwashiorkor rather than marasmus, and more likely to have diarrhea (Table 10).

A total of 64 children (3 percent) died while enrolled in the study, similar numbers in each therapeutic food group (Table 11). The expected number of fatalities based on the method of Prudhon et al. was 58. Children who died were more likely to have lower MUAC and WHZ, less likely to have kwashiorkor, and more likely to have diarrhea. Seventy-four percent of these children died within two weeks of enrollment and were not seen by the investigator after initial enrollment in the study.

Discussion

Treating severely malnourished children with a 10 percent milk RUTF results in a lower rate of recovery when compared to the standard 25 percent milk RUTF, 81 percent compared to 84 percent. Slower growth rates are seen in the children receiving the 10 percent milk RUTF as well. While this reduction is modest, it does indicate that the two formulations are not equivalent.

A limitation of this trial is that it took place in Malawi, which has a rural, primarily agrarian population and the staple food is corn. Kwashiorkor is the predominant form of severe malnutrition. Results may not be generalizable to populations where severe wasting is the predominate form of malnutrition, such as West Africa, to a non-African population, to populations with high rates of HIV infection such as South Africa, or to children living in an urban setting. Additionally, because this is a clinical effectiveness trial and not a strict efficacy trial, it cannot be assumed that children were given only the study food or that sharing within the household did not occur. It is very likely some sharing did occur.

The number of children lost to follow-up was low, just 3 percent of the total children treated, and the characteristics of the children lost to follow-up were that they were more likely to be younger and marasmic. Because the number of defaulters is so low, and the study design included randomization this

does not affect the validity of the conclusions. Default rates <10 percent are considered acceptable by international standards. The numbers of children lost to follow-up were similar in each treatment group, and thus these subjects are very unlikely to bias the findings in any way.

The results of this study are consistent with other reports of using home-based therapy with RUTF to treat severely malnourished children (Manary et al. 2004, Linneman et al. 2007, Collins et al. 2002, Ciliberto et al. 2006). This study's average recovery rate was 83 percent, while other studies in Malawi have documented recovery rates using home-based therapy with RUTF for severe malnutrition to be between 79 percent and 90 percent. In a large program in Niger, MSF found 91 percent recovery, although the prevalence of kwashiorkor in their population was only 3 percent (Defourney et al. 2006).

The children that benefit from more milk in the RUTF are children with kwashiorkor. The rate of recovery from kwashiorkor was 88 percent in children receiving 25 percent milk RUTF, compared to 85 percent in children receiving 10 percent milk RUTF, while no difference in recovery rate was seen in marasmic children receiving RUTF with more milk. Twice as many children receiving 10 percent milk RUTF required referral for inpatient care compared to those receiving 25 percent milk, and the primary reasons for referral were weight loss and worsening oedema. The two diets were isonitrogenous. If children were consuming roughly the same amount of the RUTF provided to them, these findings suggest that it was the milk protein that enhanced the resolution of oedema in kwashiorkor. All of the children in the study, however, were consuming substantial amounts of milk protein: the children receiving 25 percent milk RUTF consumed 3 g/kg/d of milk protein, while the children receiving 10 percent milk RUTF consumed 1.2 g/kg/d of milk protein. The estimated protein requirement for a well-nourished child aged 1-3 years is 1.3 g/kg/d *total* protein, from animal or plant sources.

The etiology of kwashiorkor is unknown, however a prospective dietary intake study of children at risk for kwashiorkor did not find that milk or animal protein intake was associated with the development of kwashiorkor (Lin 2007). Even though it is an unexpected finding, a large dietary intake of milk protein may facilitate resolution of oedema, while an equivalent amount of vegetable protein does not.

It is also possible that the 10 percent milk RUTF was less acceptable to the subjects; perhaps over the course of treatment the children consumed smaller amounts of 10 percent RUTF than 25 percent milk RUTF. The 10 percent milk RUTF had a darker color and a more bitter taste to the investigators who examined the product. However, of those children discharged from the study and referred for inpatient care, a larger proportion of children receiving 25 percent milk RUTF, 10/20 (50 percent) were referred because they refused to eat the food compared to the proportion receiving 10 percent milk RUTF, 7/39 (18 percent) who refused. Additionally, acceptability tests completed prior to the study did not reveal any differences; the predominant taste of RUTF is sweet, given that it is 28 percent sugar in composition. Mothers did not indicate that children consumed less 10 percent milk RUTF when questioned during follow-up visits, although this method of assessing intake has not been validated.

One advantage of substituting some soy for milk in the formulation of RUTF is that soybeans are grown throughout the world, including areas where severe malnutrition is common in sub-Saharan Africa. Locally produced RUTF could include more local ingredients by using soy, and thus be more widely available. Additionally, soy costs less than powdered milk.

Ten percent milk RUTF costs $3.80/kg and 25 percent milk RUTF costs $4.92/kg. Severely malnourished children receive on average 1.75 kg RUTF per week for a mean treatment time of four weeks. Therefore, the mean cost of one child's complete dose of 10 percent milk RUTF is $26.60 per child, and for 25 percent milk RUTF the mean cost is $34.40 per child. The costs associated with home-based therapy include paying local staff and paying for transport of the RUTF (Bachmann 2009, Caldwell et al. 2004). Funding a nurse supervisor to work at the health center in assessing and enrolling children costs $0.86 per child. Village health workers cost $1.71 per child, which covers screening and recruiting children in the community as well as enrolling children at the local health center. The fuel and vehicle required to transport RUTF to the health center, where it is accessible to people in rural communities, costs $0.59 per child. In total, non-food costs for home-based therapy are $3.20 per child. With the cost of the food, the

entire duration and treatment of a severely malnourished child with home-based therapy and 10 percent milk RUTF or 25 percent milk RUTF costs $29.80 per child or $37.60 per child, respectively.

The number needed to treat to recover one additional child with 25 percent milk RUTF compared to 10 percent milk RUTF was 34. Using the prices above for the two RUTFs at the time of the study, the additional expenditure would have been $265.20 to recover one more child.
But the relative prices of soy and milk, like all agricultural commodities, are dynamic, as evidenced by the changes in ingredient costs of RUTF during the course of this study. If the ratio of the prices of soy to milk was arbitrarily set at 1.0 in 2007, the soy:milk price ratio increased to 1.9 in 2008, and further increased to 2.5 in 2009. Over the last two years, the price of soy has risen more quickly than the price of powdered milk. The present trends in soy and milk prices reduce the savings that could be realized by substituting soy for milk in RUTF.

Approximately 15 percent of the children initially treated with home-based therapy either did not recover and were referred for inpatient therapy or died. Failure was seen most frequently in the first two weeks of therapy, marked by weight loss or worsening of oedema. The most significant risk factor for failure to recover was marasmus. In a country such as Malawi where kwashiorkor predominates, children with marasmus might benefit from a follow-up visit after seven days instead of 14 days as in this study. Alternatively, a home visit by the village health aid to children with marasmus within the first week of therapy might identify those not responding well to treatment. Identification of such children alone, however, is unlikely to improve their outcome, unless additional interventions are readily available to the children making poor progress.

A major challenge lies ahead in understanding why children with kwashiorkor responded differently—worse—to the reduced milk RUTF than those children with marasmus, for whom the reduced milk formulation performed similarly to standard RUTF. The lower recovery and growth rates seen among children with kwashiorkor consuming 10 percent milk RUTF indicate that there is an important difference in how these children respond to treatment, and therefore how they should be treated, but this difference is yet undiscernable to the nutrition community. An in-depth study of consumption patterns comparing severely malnourished children both with kwashiorkor and with marasmus may bring to light variations in how children consume and accept RUTF over the course of treatment. Alternatively, another area of study lies in more focused biochemical research exploring which hormonal responses to diet can give clues to child growth, and to ways of offering malnourished children a better chance at survival.

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Tables and Figures

Table 1. Nutrient Content of the Study Foods

Nutrient	25% milk RUTF	10% milk RUTF
Energy, *kcal/ 100g*	530	520
Protein, *g/ 100g*	15	15
Vitamin A, *µg/ 100g*	910	913
Vitamin D, *µg/ 100g*	16	16.3
Vitamin E, *mg/ 100g*	20	20
Vitamin K, *µg/ 100g*	21	21
Vitamin B1, *mg/ 100g*	0.6	0.6
Vitamin B2, *mg/ 100g*	1.8	1.8
Vitamin B6, *mg/ 100g*	0.6	0.58
Vitamin B12, *µg/ 100g*	1.8	1.85
Vitamin C, *mg/ 100g*	53	53.3
Biotin, *µg/ 100g*	65	65
Folic Acid, *µg/ 100 g*	210	210
Niacin, *mg/ 100g*	5.3	5.3
Pantothenic Acid, *mg/ 100g*	3.1	3.1
Potassium, *mg/ 100g*	1111	1110
Magnesium, *mg/ 100g*	92	92
Iron, *mg/ 100g*	11.53	11.5
Zinc, *mg/ 100g*	14	14
Copper, *mg/ 100g*	1.78	1.74
Iodine, *µg/ 100g*	110	100
Selenium, *µg/ 100g*	30	30
Calcium, *mg/ 100g*	320	300
Phosphorus, *mg/ 100g*	394	300

Table 2. Enrollment Characteristics of Children Treated for Severe Malnutrition[1]

	25% milk RUTF	10% milk RUTF	*P* Value
N	945	929	
Male, *n (%)*	432 (46)	388 (42)	0.29
Age, *mo*	19.2 ± 9.9	19.5 ± 9.7	0.50
Weight, *kg*	7.49 ± 1.75	7.50 ± 1.67	0.90
Height, *cm*	72.7 ± 7.2	72.7 ± 7.1	--
MUAC, *cm*	12.1 ± 1.3	12.2 ± 1.3	0.09
Weight for height Z-score	-2.1 ± 1.2	-2.0 ± 1.2	0.07
Weight for age Z-score	-3.1 ± 1.2	-3.1 ± 1.2	--
Height for age Z-score	-3.0 ± 1.5	-3.0 ± 1.5	--
Mother alive, *n (%)*	907/944 (96)[2]	894/929(96)	0.90
Father alive, *n (%)*	908/938 (97)	880/922 (95)	0.14
Breast-feeding, *n (%)*	555/938 (59)	539/925 (58)	0.71
Oedema, *n (%)*	737 (78)	721 (78)	0.87
Known +HIV mom, *n (%)*	44 (9)	34 (7)	0.30
Prior treatment, *n (%)*	156/937 (17)	145/922 (16)	0.61
Twins, *n (%)*	65/943 (7)	69/923 (8)	0.65
Fever, *n (%)*	524 (55)	549 (59)	0.11
Cough, *n (%)*	441 (47)	462 (50)	0.18
Diarrhea, *n (%)*	419 (44)	387 (42)	0.24
Vomiting, *n (%)*	221 (23)	209 (23)	0.66

[1] Values are means ± SD or n (%).
[2] The denominator is different from the number of children enrolled in the food group for some demographic characteristics, because these data were missing.

Table 3. Listing of Study Sites and the Numbers of Children Enrolled in Each Study Group

Study Site	Children receiving 10% milk RUTF	Children receiving 25 % milk RUTF
Chamba	74	78
Chikonde	40	44
Chikweo	81	77
Machinga	70	61
Mbiza	138	134
Mwakhila	97	101
Mlombe	48	54
Mwakwpala	26	34
Mposa	25	18
Myaka	123	137
Nkate Market	103	99
Nanunje	25	30
Ntonya	46	41
Ntaja	49	32

Table 4. Enrollment Characteristics of Children Who Defaulted Versus those Who Completed the Program[1]

	Defaulted	Completed the program	*P* value
N	51	1823	
Male, *n (%)*	17 (33)	803 (44)	0.15
Age, *mo*	22.1± 11.0	19.3 ± 9.8	0.05
Weight, *kg*	7.66 ± 1.95	7.49 ± 1.71	0.49
Height, *cm*	74.6 ± 8.3	72.7 ± 7.1	0.06
MUAC, *cm*	11.9 ± 1.5	12.2 ± 1.3	0.11
Weight for height Z-score	-2.3 ± 1.8	-2.0 ± 1.2	0.08
Weight for age Z-score	-3.3 ± 1.5	-3.1 ± 1.2	0.24
Height for age Z-score	-3.0 ± 1.9	-3.0 ± 1.5	1.00
Mother alive, *n (%)*	50/51 (98)[2]	1751/1822(96)	0.72
Father alive, *n (%)*	51/51 (100)	1737/1809 (96)	0.26
Breast-feeding, *n (%)*	27/50 (54)	1067/1813 (59)	0.56
Oedema, *n (%)*	30 (59)	1428 (78)	0.002
Known +HIV mom, *n (%)*	2 (9)	76 (8)	1.00
Prior treatment, *n (%)*	7/50 (14)	294/1809 (16)	0.85
Twins, *n (%)*	4/51 (8)	130/1815 (7)	0.78
Fever, *n (%)*	26 (51)	1047 (57)	0.39
Cough, *n (%)*	24 (47)	879 (48)	0.77
Diarrhea, *n (%)*	22 (43)	784 (43)	0.35
Vomiting, *n (%)*	15 (29)	415 (23)	0.31

[1] Values are means ± SD or n (%).
[2] The denominator is different from the number of children enrolled in the food group for some demographic characteristics, because these data were missing.

Table 5. Outcomes of Severely Malnourished Malawian Children who Received 25% Milk RUTF or 10% milk RUTF for Up to 8 Weeks[1]

Outcome	25% milk RUTF	10% milk RUTF	*P* Value
N	945	929	
Recovered, *n (%)*	790 (84)	754 (81)	0.18
Remained wasted, *n (%)*	73 (8)	83 (9)	0.36
Referred to NRU, *n (%)*	20 (2)	39 (4)	0.01
Death, *n (%)*	34 (4)	30 (3)	0.70
Lost to f/u, *n (%)*	28 (3)	23 (3)	0.57
WHZ at discharge	-1.5 ± 1.1	-1.5 ± 1.1	--
HAZ at discharge[2]	-3.1 ± 1.5	-3.2 ± 1.5	0.15
WAZ at discharge[3]	-2.7 ± 1.2	-2.8 ± 1.2	0.07
Weight gain g/kg/d week 2	2.4 ± 0.3	1.7 ± 0.3	0.70
Height gain mm/d week 2	0.16 ± 0.03	0.12 ± 0.03	0.04
MUAC gain mm/d week 2	0.18 ± 0.03	0.11 ± 0.03	0.07
Weight gain g/kg/d week 4	2.3 ± 0.2	2.3 ± 0.2	--
Height gain mm/d week 4	0.28 ± 0.03	0.25 ± 0.03	<0.001
MUAC gain mm/d week 4	0.16 ± 0.03	0.16 ± 0.03	--
Weight gain g/kg/d week 6	2.7 ± 0.3	2.2 ± 0.3	<0.001
Rate of ht gain week 6	0.28 ± 0.05	0.24 ± 0.04	0.04
MUAC gain mm/d week 6	0.17 ± 0.04	0.11 ± 0.04	0.06
Weight gain g/kg/d week 8	2.3 ± 0.5	1.7 ± 0.4	0.60
Height gain mm/d week 8	0.21 ± 0.06	0.18 ± 0.06	<0.001
MUAC gain mm/d week 8	0.12 ± 0.06	0.11 ± 0.06	0.01
Duration of treatment, *d*	28 (14,42)	28 (14,42)	--

[1] Values are means ± SD for Z-scores, or means ± 95% Confidence interval for change in weight, height or MUAC, or median (25^{th}, 75^{th} percentile) for duration of treatment. Asterisks indicate differences P<0.05:
[2] Height for age Z-score
[3] Weight for age Z-score

Table 6. Non-linear Regression Coefficients for the Analyses of Outcomes, Values Expressed as Coefficient (95% CI)

	Outcome			
Time dependent regression term	Recovery	Weight Gain	MUAC	Height Gain
Duration of treatment Weeks	-0.535 (-0.547,-0.522)*	-5.756 (-6.532,-4.981)*	-1.024 (-1.111,-0.936)*	-0.033 (-0.125,0.058)
Age months	0.002 (-0.002,-0.002)	-0.17 (-0.023,-0.011)*	-0.002 (-0.003,-0.002)*	-0.002 (-0.003,-0.001)*
Twin Yes	0.009 (0.009,0.009)*	0.263 (0.082,0.444)*	0.017 (-0.003,0.037)	0.027 (0.006,0.049)*
Sex male Yes	0.024 (-0.008,0.056)	-0.254 (-0.359,-0.148)*	-0.032 (-0.044,-0.021)*	0.002 (-0.015,0.010)
MUAC Cm	0.057 (-0.040,0.153)	0.442 (0.392, 0.493)*	0.079 (0.074,0.085)*	0.013 (0.007,0.019)*
Mother alive Yes	0.051 (0.037,0.064)*	0.094 (-0.162,0.351)	0.009 (-0.020,0.038)	0.017 (-0.014,0.047)
Father alive Yes	0.030 (0.014,0.046)*	0.070 (-0.188,0.327)	-0.004 (-0.033,0.025)	0.000 (-0.031,0.029)
Previously treated for malnutrition Yes	-0.010 (-0.042,0.022)	-0.086 (-0.214,0.043)	0.007 (-0.008,0.021)	0.011 (-0.004,0.026)
Fever on enrollment Yes	0.007 (-0.009,0.022)	-0.080 (-0.189,0.028)	-0.010 (-0.022,0.002)	-0.004 (-0.017,0.009)
Diarrhea on enrollment Yes	0.007 (-0.001,0.015)*	0.023 (-0.126,0.081)	0.001 (-0.011,0.012)	-0.007 (-0.019,0.005)
Oedema upon enrollment Yes	0.013 (0.000,0.026)*	0.132 (0.007,0.256)*	0.015 (0.001,0.029)	0.010 (-0.025,0.005)
Cough on enrollment Yes	0.004 (0.014,0.027)*	0.140 (0.034,0.245)*	0.018 (0.006,0.030)	-0.004 (-0.017,0.008)
Receiving 25% milk RUTF Yes	0.020 (0.014,0.027)*	0.147 (0.048,0.246)*	0.005 (-0.006,0.016)	0.018 (0.006,0.030)*
WHZ Z-scores	0.026 (0.013,0.039)*	-0.479 (-0.542,-0.415)*	-0.055 (-0.062,-0.048)*	0.010 (0.003,0.018)*
Feeding site	-0.002 (-0.017,0.013)	-0.003 (-0.016,0.010)	0.000 (-0.002,0.001)	0.000 (-0.002,0.001)

For the continuous time dependent regression terms (age, WHZ, MUAC and duration of treatment), positive values of coefficients mean that starting with a larger positive values of a given a parameter was associated with a better outcome, such as more recovery or greater weight gain. For dichotomous time dependent regression terms, such as receiving 25% milk RUTF or male sex, a positive coefficient value means having this quality is associated with a better outcome and a negative value is associated with a worse outcome. Coefficients with 95% CI that does not include 0 are highlighted in grey.

Table 7. Outcomes of Malawian Children with Kwashiorkor who Received 25% Milk RUTF or 10% Milk RUTF for up to 8 weeks[1]

Outcome	25% milk RUTF	10% milk RUTF	*P* Value
N	737	721	
Recovered, *n (%)*	648 (88)	613 (85)	0.10
Remained wasted, *n (%)*	34 (5)	44 (6)	0.24
Referred to NRU, *n (%)*	14 (2)	29 (4)	0.02
Death, *n (%)*	24 (3)	22 (3)	0.88
Lost to f/u, *n (%)*	17 (2)	13 (2)	0.58
WHZ at discharge	-1.2 ± 1.0	-1.3 ± 1.0	0.06
HAZ at discharge[2]	-3.1 ± 1.5	-3.2 ± 1.5	0.20
WAZ at discharge[3]	-2.6 ± 1.1	-2.6± 1.2	1.00
Weight gain g/kg/d week 2	2.0 ± 0.3	1.3 ± 0.3	<0.001
Height gain mm/d week 2	0.18 ± 0.04	0.13 ± 0.04	<0.001
MUAC gain mm/d week 2	0.17 ± 0.04	0.11 ± 0.04	<0.001
Weight gain g/kg/d week 4	2.2 ± 0.3	2.2 ± 0.3	--
Height gain mm/d week 4	0.30 ± 0.04	0.26 ± 0.04	<0.001
MUAC gain mm/d week 4	0.17 ± 0.03	0.16 ± 0.04	<0.001
Weight gain g/kg/d week 6	2.5 ± 0.4	2.1 ± 0.4	<0.001
Rate of ht gain week 6	0.28 ± 0.06	0.24 ± 0.05	<0.001
MUAC gain mm/d week 6	0.16 ± 0.05	0.11 ± 0.05	<0.001
Weight gain g/kg/d week 8	2.2 ± 0.6	1.9 ± 0.5	<0.001
Height gain mm/d week 8	0.18 ± 0.07	0.16 ± 0.08	<0.001
MUAC gain mm/d week 8	0.10 ± 0.08	0.13 ± 0.08	<0.001
Duration of treatment, *d*	28 (14,42)	28 (14,42)	--

[1] Values are means ± SD for Z-scores, or means ± 95% Confidence interval for change in weight, height or MUAC, or median (25^{th}, 75^{th} percentile). Asterisks indicate differences P<0.05:
[2] Height for age Z-score
[3] Weight for age Z-score

Table 8. Outcomes of Malawian Children with marasmus who Received 25% Milk RUTF or 10% Milk RUTF for Up to 8 Weeks[1]

Outcome	25% milk RUTF	10% milk RUTF	*P* Value
N	208	208	
Recovered, *n (%)*	142 (68)	141 (68)	0.99
Remained wasted, *n (%)*	39 (19)	39 (19)	--
Referred to NRU, *n (%)*	6 (3)	10 (5)	0.45
Death, *n (%)*	10 (5)	8 (4)	0.81
Lost to f/u, *n (%)*	11 (5)	10 (5)	0.99
WHZ at discharge	-2.3 ± 0.9	-2.5 ± 0.9	0.02
HAZ at discharge[2]	-3.3 ± 1.6	-3.2 ± 1.5	0.51
WAZ at discharge[3]	-3.4 ± 1.1	-3.5 ± 1.1	0.35
Weight gain g/kg/d week 2	4.0 ± 0.5	2.9 ± 0.6	<0.001
Height gain mm/d week 2	0.07 ± 0.06	0.07 ± 0.06	--
MUAC gain mm/d week 2	0.23 ± 0.07	0.10 ± 0.07	<0.001
Weight gain g/kg/d week 4	2.6 ± 0.6	2.8 ± 0.5	<0.001
Height gain mm/d week 4	0.22 ± 0.06	0.19 ± 0.06	<0.001
MUAC gain mm/d week 4	0.13 ± 0.07	0.18 ± 0.05	<0.001
Weight gain g/kg/d week 6	3.4 ± 0.7	2.5 ± 0.6	<0.001
Rate of ht gain week 6	0.27 ± 0.07	0.22 ± 0.07	<0.001
MUAC gain mm/d week 6	0.18 ± 0.07	0.11 ± 0.06	<0.001
Weight gain g/kg/d week 8	2.4 ± 0.7	1.4 ± 0.8	1.00
Height gain mm/d week 8	0.26 ± 0.12	0.22 ± 0.09	<0.001
MUAC gain mm/d week 8	0.16 ± 0.08	0.09 ± 0.09	<0.001
Duration of treatment, *d*	28 (14,42)	28 (14,42)	--

[1] Values are means ± SD for Z-scores, or means ± 95% Confidence interval for change in weight, height or MUAC, or median (25^{th}, 75^{th} percentile) for duration of treatment. Asterisks indicate differences P<0.05:
[2] Height for age Z-score
[3] Weight for age Z-score

Table 9. Characteristics of Children Referred for Inpatient while Receiving Home-Based Therapy with RUTF

	25% milk RUTF N = 20	10% milk RUTF N = 39	*P* value
Significant weight loss	13/20 (65%)	17/39 (44%)	0.17
Worsening oedema	3/20 (15%)	10/39 (26%)	0.51
Refused to eat RUTF	10/20 (50%)	7/39 (18%)	0.02
Vomiting	4/20 (20%)	6/39 (15%)	0.48
Diarrhea	4/20 (20%)	11/39 (28%)	0.55
Oral Thrush	0/20 (0%)	2/39 (5%)	0.54

P values determined using Fisher's Exact Test

Table 10. Enrollment Characteristics of Children who Recovered Compared to Children who Failed Treatment[1]

	Recovered	Failed treatment	*P* value
N	1544	330	
Male, *n (%)*	687 (45)	133 (40)	0.24
Age, *mo*	19.3 ± 9.7	19.4 ± 10.1	0.87
Weight, *kg*	7.62 ± 1.67	6.93 ± 1.78	< 0.001
Height, *cm*	72.9 ± 7.0	71.9 ± 7.9	0.02
MUAC, *cm*	12.3 ± 1.3	11.4 ± 1.3	< 0.001
Weight for height Z-score	-1.9 ± 1.2	-2.7 ± 1.3	< 0.001
Weight for age Z-score	-2.9 ± 1.2	-3.7 ± 1.2	< 0.001
Height for age Z-score	-3.0 ± 1.5	-3.3 ± 1.6	0.001
Mother alive, *n (%)*	1493/1543 (97)[2]	308/330(93)	0.01
Father alive, *n (%)*	1481/1533 (97)	307/327 (94)	0.02
Breast-feeding, *n (%)*	915/1535 (60)	179/328 (55)	0.10
Oedema, *n (%)*	1261 (82)	197 (60)	< 0.001
Mother HIV+, *n (%)*	64 (8)	14 (8)	0.88
Prior treatment, *n (%)*	239/1533 (16)	62/326 (19)	0.14
Twins, *n (%)*	113/1537 (7)	21/329 (6)	0.64
Fever, *n (%)*	885 (57)	188 (57)	0.95
Cough, *n (%)*	731 (47)	172 (52)	0.13
Diarrhea, *n (%)*	639 (41)	167 (51)	0.003
Vomiting, *n (%)*	340 (22)	90 (27)	0.04

[1] Values are means ± SD or n (%).
[2] The denominator is different from the number of children enrolled in the food group for some demographic characteristics, because these data were missing.

Table 11. Enrollment Characteristics of Children Who Died Compared to Children Who Survived[1]

	Survived	Died	*P* value
N	1810	64	
Male, *n (%)*	794 (44)	26 (41)	0.70
Age, *mo*	19.3 ± 9.7	19.3 ± 12.0	0.99
Weight, *kg*	7.52 ± 1.69	6.80 ± 2.05	< 0.001
Height, *cm*	72.8 ± 7.0	71.1 ± 9.0	0.06
MUAC, *cm*	12.2 ± 1.3	11.2 ± 1.3	< 0.001
Weight for height Z-score	-2.0 ± 1.2	-2.7 ± 1.3	< 0.001
Weight for age Z-score	-3.1 ± 1.2	-3.8 ± 1.1	< 0.001
Height for age Z-score	-3.0 ± 1.5	-3.4 ± 1.3	0.04
Mother alive, *n (%)*	1742/1809 (96)[2]	59/64 (92)	0.10
Father alive, *n (%)*	1729/1798 (96)	59/62 (95)	0.73
Breast-feeding, *n (%)*	1060/1799 (59)	34/64 (53)	0.37
Oedema, *n (%)*	1412 (78)	46 (72)	0.009
Known +HIV mom, *n (%)*	75 (8)	3 (13)	0.75
Prior treatment, *n (%)*	295/1795 (16)	6/64 (9)	0.17
Twins, *n (%)*	132/1802 (7)	2/64 (3)	0.32
Fever, *n (%)*	1038 (57)	35 (55)	0.41
Cough, *n (%)*	863 (48)	40 (63)	0.01
Diarrhea, *n (%)*	764 (42)	42 (66)	< 0.001
Vomiting, *n (%)*	412 (23)	18 (28)	< 0.001

[1] Values are means ± SD or n (%).
[2] The denominator is different from the number of children enrolled in the food group for some demographic characteristics, because these data were missing.

Figure 1. Subject Enrollment Flowchart

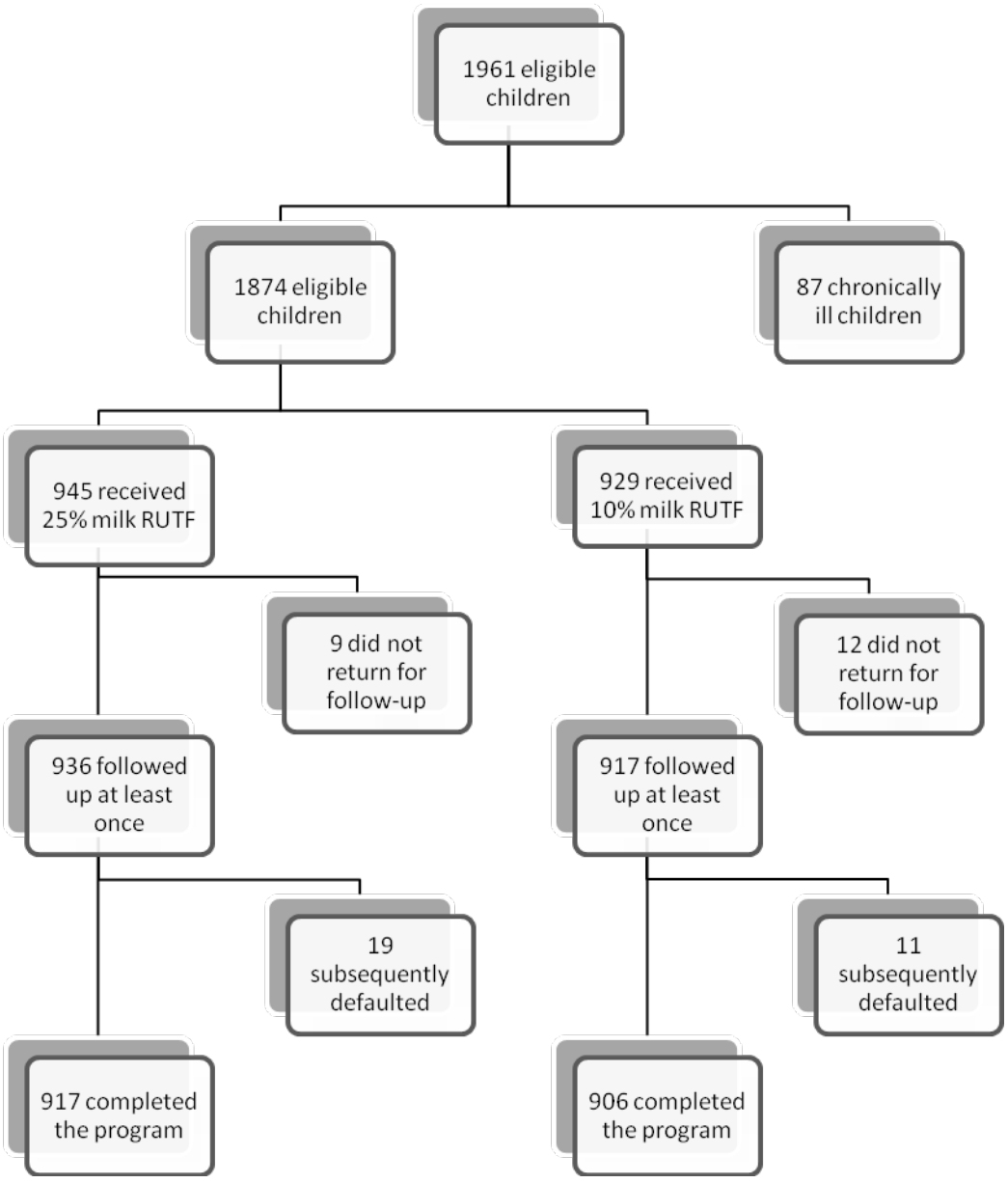
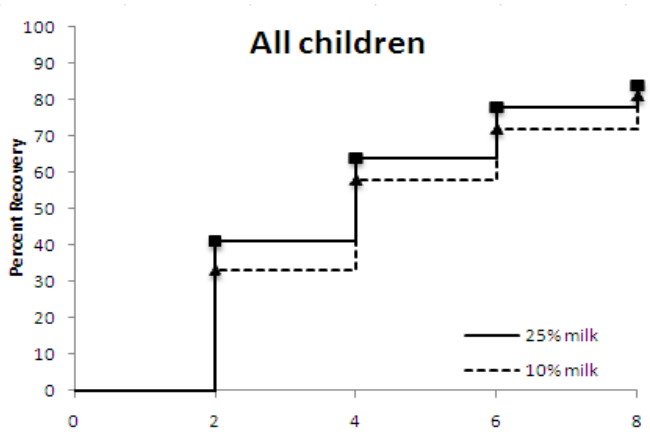
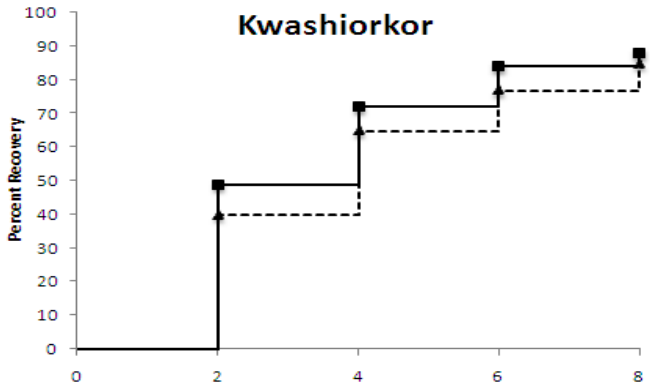


Figure 2. Recovery rates for Malawian children who received 25% milk RUTF or 10% milk RUTF for all severely malnourished children (panel A), children with kwashiorkor (panel B), and children with marasmus (panel C). Recovery was defined as meeting target WHZ and having no oedema on the same day.

A.



B.



C.

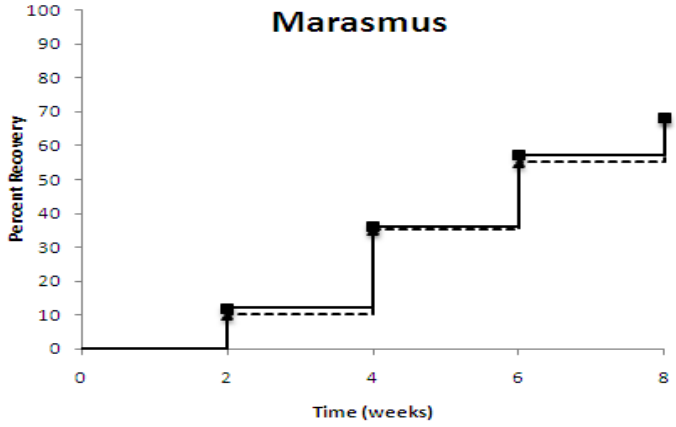
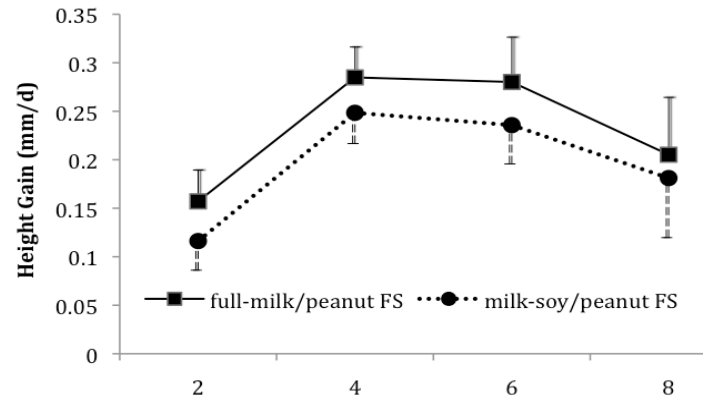


Figure 3. Rates of gain in stature (A), MUAC (B), and weight (C) for all severely malnourished Malawian children who received 25% milk RUTF or 10% milk RUTF for up to 8 weeks. Values are means, whiskers are 95% CI.

A. All Children



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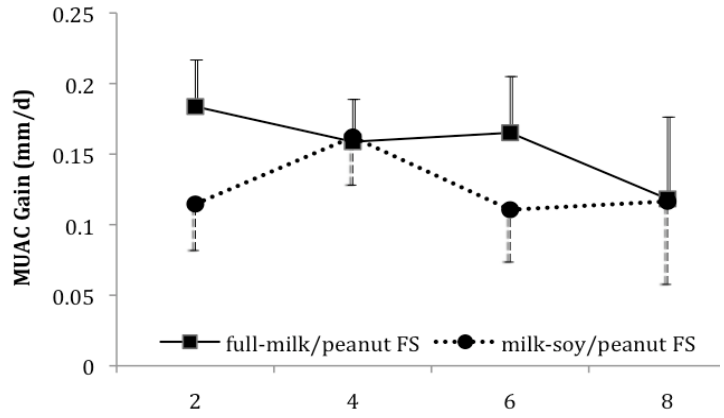

C.

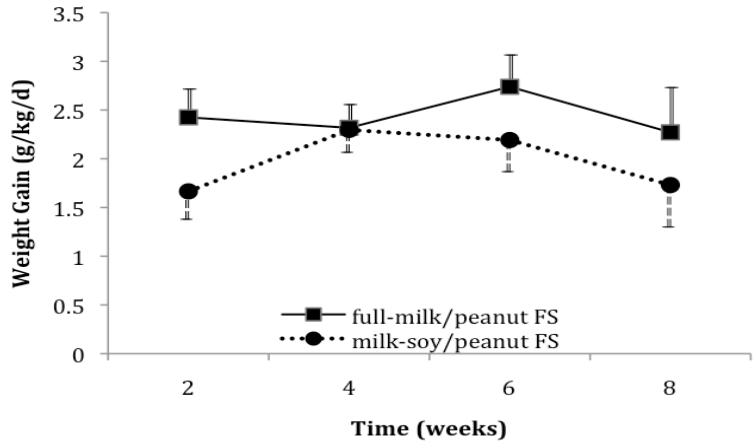

Figure 4. Rates of gain in stature (A), MUAC (B), and weight (C) for Malawian children with kwashiorkor who received 25% milk RUTF or 10% milk RUTF for up to 8 weeks. Values are means, whiskers are 95% CI.

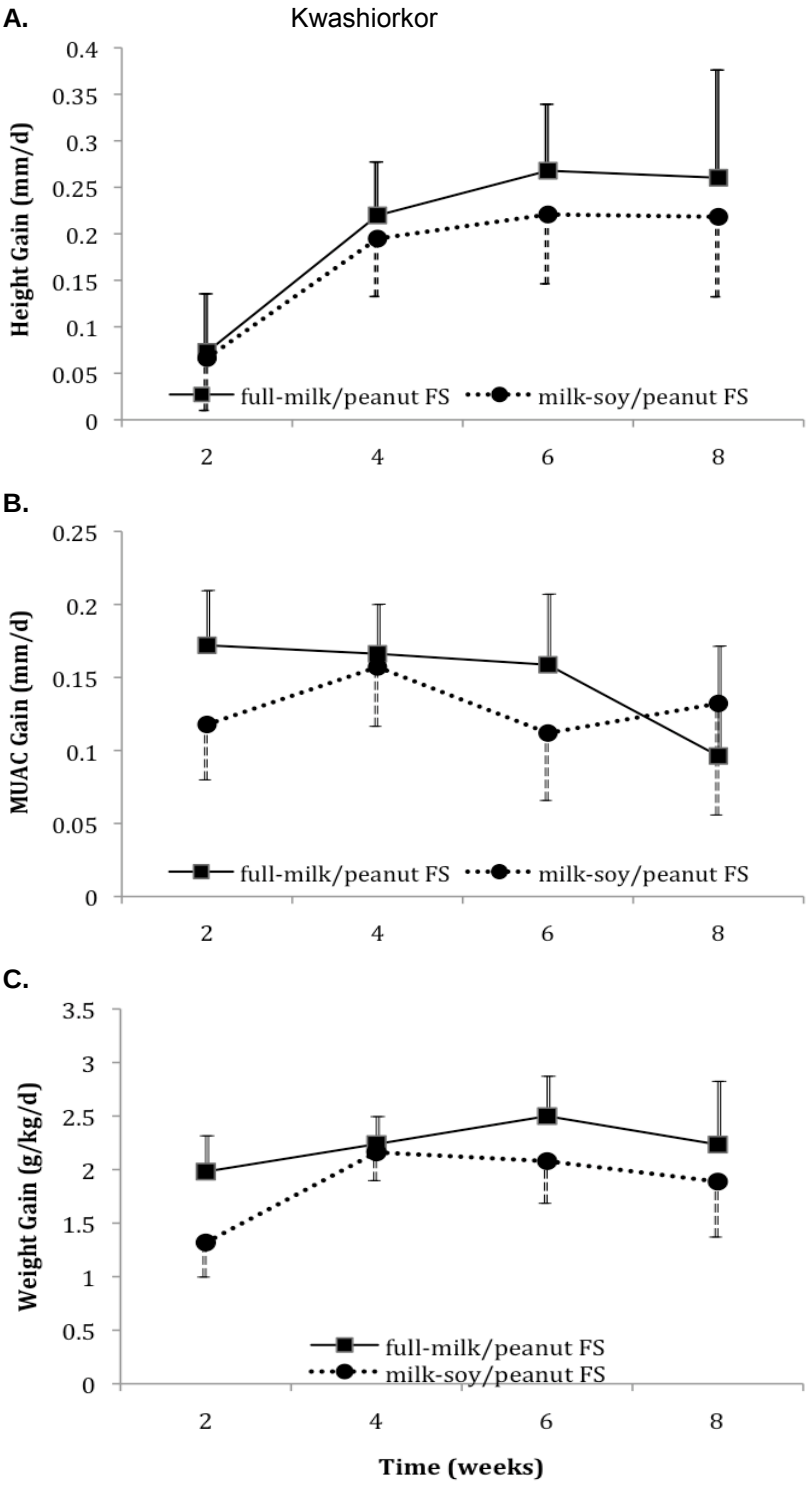

Figure 5. Rates of gain in stature (A), MUAC (B), and weight (C) for Malawian children with marasmus who received 25% milk RUTF or 10% milk RUTF for up to 8 weeks. Values are means, whiskers are 95% CI.