Rethinking Recovery:
Generating evidence to improve and sustain recovery from moderate acute malnutrition in children

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Abstract

This dissertation focuses on interventions that are intended to result in improved and sustained recovery from moderate acute malnutrition (MAM) in children. Research was conducted in southern Malawi with children between ages 6 and 62 months with MAM, defined as having a mid-upper arm circumference (MUAC) 11.5-12.4 cm, and with children immediately following initial recovery from MAM.

The aim of the research presented in Chapter 1 was to measure effectiveness and cost-effectiveness of including whey protein in a ready-to-use supplementary food (RUSF) used to treat MAM. In a double-blinded, randomized controlled trial comparing a soy RUSF and a whey RUSF, the proportion of children that recovered from MAM was higher in the group that received whey RUSF (84%) compared to soy RUSF (81%). The whey RUSF group also demonstrated higher MUAC at discharge, greater MUAC gain and weight gain during treatment, and higher weight-for-height Z-score (WHZ) at discharge. A cost-effectiveness analysis revealed that substituting whey RUSF for soy RUSF resulted in a $0.42 decrease in the total programmatic cost per child recovered ($54.76 and $54.34 for soy and whey RUSF, respectively).

Chapter 2 presents a cluster randomized controlled trial to measure the effectiveness of a package of health and nutrition interventions—consisting of a lipid nutrient supplement (LNS), deworming medication, a zinc supplement, a bed net, and malaria chemoprophylaxis—in improving the proportion of children who sustain recovery for one year following treatment for MAM. The proportion of children who sustained recovery for one year was higher in the intervention group. Larger MUAC at the start of treatment, larger increase in MUAC during treatment, and higher WHZ at the end of treatment were the strongest predictors of sustained recovery. The type of food (whey RUSF vs. soy RUSF) consumed during treatment was not predictive of relapse when controlling for other factors. Nearly all serum C3 levels, a proxy for immune function, were normal at discharge. Half of all relapses occurred within three months of initial recovery. Poor linear growth following recovery was found to be significantly associated with relapse.

Chapter 3 consists of a sub-study from the study in Chapter 2. The aim was to identify household factors, collected in an in-depth household survey, associated with sustained recovery following MAM treatment. Results showed improved WASH indicators were associated with a child sustaining recovery, yet indicators relating to socioeconomic status, food security, and infant and young child feeding practices were not.

In conclusion, this dissertation presents evidence that suggests a uniform approach for treating all children with MAM may not be appropriate to achieve sustained recovery. Also, incorporating higher discharge MUAC cut-offs, post-discharge monitoring, earlier identification of children with MAM, and additional preventive services should be integrated into MAM treatment to reduce the risk of relapse. Although consuming whey RUSF compared to soy RUSF resulted in modestly improved recovery rates, the type of treatment food did not affect relapse rates. Future studies are needed to identify possible underlying physiological factors that may not have fully recovered at SFP discharge.

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Introduction

The overall purpose of this dissertation is to document the effects of innovative interventions aimed at improving and sustaining recovery from moderate acute malnutrition (MAM) in children. The primary focus is on identifying treatment factors to increase initial recovery rates and sustained recovery for one year following MAM treatment. This was done by measuring the effectiveness of different types of treatment for MAM, including the use of whey in treatment foods and the provision of additional services following treatment, on initial and sustained recovery. Individual child and household level factors were explored to identify possible risk factors of relapse. Results presented in this dissertation aim to fill current gaps in knowledge regarding the effectiveness and sustainability of MAM treatment and contribute to the development of future evidence-based protocols.

While international agencies have created recommended best practices in the management of MAM, evidence is limited regarding what treatment is necessary for children suffering from MAM to reach sustained recovery without poor post-discharge outcomes such as relapse to MAM, development of severe acute malnutrition (SAM), illness, and death. One important aspect of treatment that requires clarification is the optimal amount and type of protein in supplementary foods that produces the highest impact in both immediate recovery and longer-term outcomes. This includes measuring the effectiveness and cost-effectiveness of replacing soy protein with whey protein in supplementary foods. Furthermore, few studies have systematically followed children after discharge, proving a great need to better understand the health and nutrition of children who are discharged from MAM treatment and the sustainability of recovery.

The first study presented in Chapter 1 explores the impact of using a supplementary food that contains whey, an animal-sourced protein, with a supplementary food containing soy, a plant-based protein, on the recovery from MAM. Nutrition experts and policy makers have recently advocated for the inclusion of animal-sourced protein, specifically whey, into supplementary foods (1); however, evidence specifically supporting the inclusion of whey in supplementary foods for treating malnourished children is limited (2). Due to the need for keeping costs of supplementary foods low, evidence is needed to justify the increased expense of including whey in products used for treating children with MAM. Chapter 1 presents results from a double-blind, randomized controlled clinical effectiveness trial that compares two ready-to-use supplementary foods (RUSF)—a soy-based RUSF versus a whey-based RUSF—in the treatment of children with MAM. While results presented in Chapter 1 focus on immediate recovery rates, Chapter 2 explores if the different types of supplementary foods affect relapse rates following initial recovery from MAM.

Chapter 2 focuses on research to better understand the longer-term health and nutritional status of children who successfully recover from MAM by testing an intervention delivered at discharge aimed to sustain recovery over a period of one year. Current evidence from the limited number of studies that have systematically followed children after discharge from supplementary feeding programs (SFP) show that children who recover from MAM remain at high-risk for relapsing to MAM, developing SAM, and mortality. For example, a study in Malawi by Chang et al. (3) found only 63% of children successfully treated for MAM sustained recovery during the subsequent 12 months, while 17% relapsed to MAM, 10% developed SAM, and 4% died. The study in Chapter 2 was designed to complement this previous research and build upon the small body of knowledge regarding children after discharge from an SFP. Here, we assessed whether a package of simple and affordable health and nutrition interventions provided to children who recover from MAM can increase the proportion of children who sustain recovery (defined as maintaining MUAC $\geq$ 12.5 cm) continuously for one year following treatment. We also examined factors that may be predictive of whether or not recovery is sustained, including clinical signs of illness, anthropometric measurements, and immune function during and after SFP treatment. Furthermore, we investigated patterns of multiple relapses, the impact of seasonality on relapse, and the relationship between relapse and linear growth.

Chapter 3 examines household level factors that may be associated with relapse following recovery from MAM. It is plausible that discharging children back into the same household environment that may have been influential in the development of malnutrition in the first place may also play a role in relapse. Identifying household risk factors for relapse could have significant implications on how best to prevent relapse and improve the sustainability of recovery from MAM. To identify such factors, we analyzed data from an in-depth household survey on a sub-sample of participants in the cluster-randomized controlled trial presented in Chapter 2.

References:

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Literature Review

Moderate acute malnutrition

According to the 2016 World Health Statistics report, almost 33 million children worldwide suffer from moderate acute malnutrition (MAM), or moderate wasting, defined as weight-for-height z score (WHZ) < −2 and ≥ −3 standard deviations (SD) (1). Black et al. (2) in a 2013 Lancet nutrition series estimates that acute malnutrition, including both MAM and severe acute malnutrition (SAM) (defined as WHZ < −3 SD), account for approximately 11.5% of total deaths of children under 5 years old. South Asia has the largest prevalence and number of children with MAM, followed by Africa and the Middle East (**Table 1**) (3).

Table 1. Number of children (in millions) suffering from acute malnutrition, moderate acute malnutrition (MAM), and severe acute malnutrition (SAM) in 2015.

	Asia	Africa	Latin America and Caribbean	Oceania	Total
Acute Malnutrition	33.9	14.1	0.7	0.1	48.8
MAM	22	9.8	0.5	0.06	32.4
SAM	11.9	4.3	0.2	0.04	16.4

Source: UNICEF, WHO, World Bank Group joint malnutrition estimates, 2016 edition. Excluding Australia, New Zealand, and Japan. HAZ, height-for-age z-score; SD, standard deviation; WHZ, weight-for-height z-score.

United Nations Children's Fund (UNICEF), World Health Organization (WHO), World Bank Group joint malnutrition estimates reveal worldwide numbers of children who suffer from acute malnutrition have only marginally decreased over the years, particularly when compared to progress made in reducing other malnutrition indicators, such as stunting (4). A review by Annan et al. (5) in 2014 states the global estimated number of children suffering from MAM and SAM was only reduced by 11% over the course of 21 years, between 1990 and 2011. From more recent available data between 2010-2015, 20 countries had a nation-wide acute malnutrition prevalence above the WHO's threshold of 15%, representing a "public health emergency requiring immediate intervention" (4). The country with the highest prevalence is South Sudan where almost one in four children experience MAM or SAM, while India has the highest burden in absolute numbers with approximately 19 million acutely malnourished children (**Table 2**) (4).

Table 2. Top 12 countries with acute malnutrition (MAM and SAM) and moderate acute malnutrition (MAM) in children 6-59 months

Country	Year	Acute Malnutrition (SAM and MAM) (%)	Moderate Acute Malnutrition (MAM) (%)	Total Children with Acute Malnutrition (SAM and MAM) (thousands)
South Sudan	2010	23	13	375.8
Djibouti	2012	22	12	21.5
Sri Lanka	2012	21	18	372.8
Niger	2012	19	12	689.4
Bangladesh	2013	18	13	2,787.7
Nigeria	2013	18	9	5,396.7
Sudan	2014	16	12	957.9
Yemen	2014	16	11	633.3
Chad	2010	16	10	363.3
Burkina Faso	2010	15	10	440.0
Eritrea	2010	15	11	119.4
India	2014	15	11	18,790.6

Source: UNICEF, WHO, World Bank Group joint malnutrition estimates, 2016 edition. GAM, global acute malnutrition; MAM, moderate acute malnutrition. Data available at: http://data.unicef.org/resources/child-nutrition-interactive-dashboard-2015-edition/

The immediate consequences of MAM and SAM are life threatening. In a Lancet series on nutrition in 2008, Black et al. (6) revealed that those with SAM are approximately ten times more likely to die than a child with a WHZ > −1 SD. MAM alone presents a risk of death three times higher than well-nourished children, with increased likelihood of disease and the development of SAM (6). While children with SAM carry a higher risk of mortality, nearly twice as many children suffer from MAM worldwide (**Table 1**). Children with MAM can quickly deteriorate to having SAM, and also, MAM can persist for several months. A prospective cohort study by James et al. (7) in Ethiopia found that among children who went untreated for MAM, 10% developed SAM, and over 33% remained with MAM for at least seven months.

Much of the mortality risk associated with MAM derives from co-morbidities, such as infectious and chronic diseases like HIV, tuberculosis, malaria, pneumonia, and others. As explained in a systematic review of malnutrition and disease by Rytter et al. (8), the general relationship between infection and malnutrition is cyclical in nature: infections exacerbate malnutrition, while malnutrition suppresses immunity. For example, inadequate intake can lead to deficiencies in zinc, iron, and Vitamin A, all of which negatively affect immune function and increase risk of disease. The immune system requires higher energy intake to combat disease, yet infections often inhibit intake of nutrients through impaired absorption, decreased appetite, and increased excretion with diarrhea.

What happens to children following initial recovery from MAM?

Relapse and mortality following recovery from MAM

While the vast majority of research conducted around MAM addresses the causes, short-term risks, and immediate recovery of MAM, little is known about the overall health and nutrition of children following recovery. Few studies have systematically followed children after treatment for MAM, yet those that have been done found that relapse back to MAM, the development of SAM, and mortality were common. A study in Niger by Nackers et al. (9) in 2010 followed children for 6 months after successful discharge from MAM treatment and compared post-discharge outcomes between those receiving a ready-to-use therapeutic food (RUTF) and those receiving corn-soy-blend (CSB) during treatment. Approximately 62% of all children sustained recovery (RUTF at 62.9% and CSB at 61.2%), while 20% relapsed to MAM (RUTF at 19.4% and CSB at 21.7%), 1 % died (RUTF at 1.8% and CSB at 0%), and 16% were lost to follow-up (RUTF at 15.9% and CSB at 17.1%) after six months. Another study in Malawi by Chang et al. (10) in 2013 found that only 63% of children treated for MAM sustained recovery during the subsequent year, while 17% relapsed to MAM, 10% developed SAM, and 4% died. Chang et al. state that a 4% death rate of children following recovery from MAM is 4 times higher than the country's expected mortality rate among children aged 1–5 years. In Burkina Faso, a more recent follow-up study by Somassè et al. (11) consisting of 90% children with MAM and 10% children with SAM reported relapse rates (to MAM or SAM) close to 15%. In this study, more than one-third of the children were lost to follow-up, suggesting possibly an even higher rate of relapse or death.

High relapse and mortality rates have also been seen in children following recovery from SAM. In Bangladesh, Ashraf et al. (12) found that 18% of children relapsed within six months of discharge from SAM treatment. A coverage survey administered in Nigeria in 2013 reported that 25% of children had relapsed within 12 months after being discharged as recovered from a community-based management of acute malnutrition program (13). In an analysis of mortality after SAM recovery using data from Bangladesh, Kenya, Malawi and Niger, Bahwere et al. (14) showed the risk of death was highest during and immediately after treatment, then lessened over time. The Somassè et al. (11) study in Burkina Faso that followed children who recovered from MAM and SAM found that children with SAM were more likely to die after discharge than children with MAM. This is also seen in another study by Kerac et al. (14) in 2014 in Malawi, where results showed high rates of post-discharge mortality (25%) one year after recovery from SAM in an inpatient treatment facility.

Illness following recovery from MAM

Both the Chang et al. (10) study (following MAM children after recovery in Malawi) and the Ashraf et al. (12) study (following SAM children after recovery in Bangladesh) observed illness to be common after initial recovery. Ashraf et al. (12) reported that illnesses, such as fever, cough, malaria, and diarrhea, were frequently present during the initial three months after discharge, then decreased thereafter. Two weeks after discharge, children experiencing diarrhea, cough, fever, or "another illness" ranged from 20-24%, with 16% requiring medication. Authors point out that morbidity rates were significantly higher among children recovering from SAM even when compared to other children recovering from severe pneumonia. Chang et al. (10) found that fever, diarrhea, and malaria were reported as the cause of death for 79% of children who died following initial recovery from MAM. Results from the same study also showed relapse occurred most during the peak malaria season. These results suggests that the same common infectious diseases that often afflict non-malnourished children in resource limited settings may play a role in causing children who have recently recovered from MAM to relapse and die.

Poor linear growth following recovery from MAM

Poor linear growth and short stature have also been observed in children after recovery from MAM and SAM. The Chang et al. (10) study (following MAM children after recovery in Malawi) identified short stature during initial MAM treatment was associated with later relapsing to MAM, developing SAM, and death one year following initial recovery. In a second study by Nackers et al. (9) in Niger, results showed minimal height gain (an average of 0.17 and 0.16 change in height-for-age z-score (HAZ) for children who had received RUTF and CSB, respectively) during the first six months following MAM recovery. No statistical difference was observed in linear growth between the two groups receiving different supplementary foods.

Regarding children with SAM in Bangladesh, Ashraf et al. (12) found children remained severely stunted (with an average HAZ remaining < -3) throughout the entire six months following SAM recovery, despite improvement in WHZ scores. These results were consistent with that of Bahwere et al. (15) who observed persistent post-SAM stunting in a review of four follow-up studies in Bangladesh, Kenya, Malawi and Niger. Also, the Kerac et al. (14) study following children for one year after SAM treatment in Malawi found that SAM survivors showed good improvement in weight-for-height growth, but linear growth remained poor (with an average HAZ of -2.97) one year following recovery. In the same study, HAZ upon admission to treatment was lower among those who died within one year after SAM discharge compared to those who survived. The effects of poor linear growth following MAM and SAM recovery may be long lasting. A 2016 study in Malawi by Lelijveld et al. (16) followed survivors of SAM for seven years after initial recovery and found significantly more stunting in SAM survivors than siblings and other children in the same community. Similar longitudinal studies are needed that follow MAM children for several years after recovery in order to determine if poor linear growth persists later in life.

In contrast to these findings, some research has shown that linear growth can improve during and following treatment for SAM and MAM. Two studies, by Doherty et al. (17) in Bangladesh and Walker and Golden (18) in the West Indies, confirmed that improved linear growth can occur, but does so only after treatment for acute malnutrition begins. Results differed, however, as to whether linear growth began during initial treatment, as seen in the Doherty et al. (17) study, or only after reaching a weight gain threshold, as observed by Walker and Golden (18). Still, further research is needed to better understand why some children experience improved linear growth, while others show minimal or no linear growth during and after recovery from MAM.

Potential longer-term consequences of MAM

Although research conducted in this dissertation is limited to examining initial recovery and post-discharge outcomes within one year after recovery, it is worth noting that potential longer-term consequences of MAM may occur. To date, no studies have systematically followed children after treatment for MAM for longer than one year. However, knowledge can be gleaned from a recent cohort study by Lelijveld et al. (16) in 2016 that assessed children seven years after recovery from SAM in Malawi. Compared to individuals who did not experience SAM during childhood, survivors of SAM were more likely to have shorter stature (lower HAZ) smaller mid-upper arm, hip, and calf circumferences, less lean mass, more functional impairments, and lower school achievement. Another potential long-term outcome identified by Lelijveld et al. (16) is an increased risk for non-communicable diseases later in life. Although nutrition experts Briend and Berkley (19) in a 2016 commentary article warn this finding requires further clinical trials to determine if the associated adult diseases are caused specifically by SAM as opposed to other health and nutrition deficits in childhood known to be linked to adult health. Still, longer-term impacts of MAM are certainly plausible and longitudinal studies are needed to identify them in order to best create treatment and prevention protocols that promote sustained recovery and improved longer-term outcomes.

Current Treatment of MAM

While no single set of international standards exists for the treatment of MAM, several agencies have recommended principles and decision-making tools to facilitate best practices. These include: WHO, UNICEF, WFP, UNHCR consultation on the programmatic aspects of the management of moderate malnutrition in children under five years of age (20); the Global Nutrition Cluster's publication on Moderate Acute Malnutrition: A Decision Tool for Emergencies (21); Harmonised Training Package module 12 on MAM management (22); UNHCR Operational Guidance on the use of special nutritional products in refugee populations (23); UNHCR/WFP Guidelines for Selective Feeding: The Management of MAM in Emergencies (24); and WHO's Technical Note on Supplementary Feeding for the Management of MAM (25). **Table 3** contains a brief overview of some recommended principles regarding the treatment of MAM.

Table 3. Recommended principles for the treatment of MAM

1. Every child should receive nutrition of a sufficient quality and quantity to enable normal growth and development
2. Children 6–59 months of age with MAM need to receive nutrient-dense foods to meet their extra needs for weight and height gain and functional recovery
3. Animal-sourced foods should be provided when possible as they are more likely to meet the amino acid and other nutrient needs of recovering children. Plant-sourced foods, in particular legumes or a combination of cereals and legumes, also have high-quality proteins, although they contain some anti-nutrients
4. Supplementary foods, particularly when they represent the main source of energy, need to provide nutrients at levels that do not cause adverse effects in children with MAM when consumed for several months.
5. Management of MAM in children 6–59 months of age should include nutrition counseling regarding essential nutrition actions

Source: Adapted from Annan R, Webb P, Brown R. Management of moderate acute malnutrition (MAM): current knowledge and practice. CMAM Forum Technical Brief: September 2014. CMAM Forum, 2014.; WHO. Technical note: supplementary foods for the management of moderate acute malnutrition in infants and children 6–59 months of age. Geneva, World Health Organization, 2012.

Nutrition Counseling

An ideal approach for preventing and treating MAM includes nutrition counseling that guides caregivers to provide a suitable diet with appropriate breastfeeding practices. For proper growth and recovery to occur, a relatively wide variety of nutrient-rich and energy dense foods is required, including staple cereals, legumes, animal-sourced foods, vegetables, fruits, and oils. However, the diet among many populations where MAM is prevalent consists primarily of plant-based foods high in antinutrients, such as dietary fiber and phytates that inhibit proper absorption of several nutrients. Therefore, due to wide-scale food insecurity and the subsequent inability for poor households to achieve appropriate dietary diversity, governments and international agencies frequently use specially formulated foods to try and meet the needs of children suffering from MAM.

Supplementary Feeding Programs

Most of the programs designed to treat MAM consist of providing specially formulated foods in an outpatient based, supplementary feeding program (SFP). SFPs are often incorporated within larger community interventions, called the community-based management of acute malnutrition (CMAM) approach, where they are ideally linked with inpatient and outpatient care of severely malnourished children. While in the SFP, children with MAM return weekly or bi-weekly for assessment and collection of the next ration of food until the child is discharged as recovered from MAM or reaches a maximum length of stay in the program. Recovery is typically defined by achieving a certain threshold in growth, measured by either MUAC or WHZ. It is not common for any routine follow-up procedures or additional services to take place once a child is discharged.

The exact nutritional needs of children suffering from MAM are still unknown. A proposed nutrient composition for appropriate recovery is estimated by Golden (26) to be somewhere between that which is needed for recovery from SAM and well-nourished children. Based on this estimate, WHO recently released a recommended composition for specially formulated foods used in the treatment of MAM (**Table 4**) (25). Further trials are needed to confirm these recommendations.

Table 4. Proposed nutrient composition of supplementary foods for us in the management of moderate acute malnutrition in children[1]

Nutrient per 1000 kcal	**Unit**	**Minimum**	**Maximum**
Protein	g	20	43
Fat	g	25	65
omega-6 fatty acid	% energy	> 4.5	< 10
omega-3 fatty acid	% energy	> 0.5	< 3
trans-fatty acid	% total fat		3
Minerals			

Sodium (Na)	mg	-	500
Potassium (K)	mg	1500	2200
Magnesium (Mg)	mg	280	420
Phosphorus (P)	mg	850	1400
Zinc (Zn)	mg	20	35
Calcium (Ca)	mg	1000	1400
Copper (Cu)	mg	1	3.5
Iron (Fe)	mg	18	30
Iodine (I)	µg	150	350
Selenium (Se)	µg	35	90
Manganese (Mn)	mg	1	2
Vitamins			
Thiamin (B1)	mg	> 1	-
Riboflavin (B2)	mg	> 4	-
Pyridoxine (B6)	mg	> 2	-
Cobalamine (B12)	µg	> 5	-
Folate	µg	> 400	-
Niacin	mg	> 25	-
Ascorbate (vitamin C)	mg	> 150	-
Pantothenic Acid	mg	> 5	-
Biotin	µg	> 20	-
Retinol (27)	µg	2000	3000
Cholecalciferal vitamin D	µg	20	60
Vitamin E (α tocopherol acetate)	mg	> 30	-
Phytomenadione vitamin K	µg	> 50	-
Rations of nutrients (based on weight)			
Ca/P ratio		1	1.5
Zn/Cu ratio		5	20
Zn/Fe ration		0.8	3.5
Vitamin C/Fe		3	16

[1]The suggested concentrations are calculated as an example when supplementary foods provide 70% of energy. This does not constitute a recommendation that supplementary foods should provide 70% of the energy intake of moderately malnourished children. The formulation is such that it would be safe and effective if the quantity taken by moderately malnourished children represented 100% of the energy needs and that it would also provide benefit, although of a lesser order of magnitude, if taken in lower quantities. There is no evidence to determine maximum levels for some nutrients. In countries with established maximum levels for these nutrients in healthy children, it would appear convenient to use those amounts to inform product formulation. The energy density of supplementary foods when they are ready to be

consumed should be not less than 0.8 kcal/g. Protein digestibility-corrected amino acid score >70%. Corresponds to cereal/legume mixtures, milk and animal proteins.
Source: WHO. Technical note: supplementary foods for the management of moderate acute malnutrition in infants and children 6–59 months of age. Geneva, World Health Organization, 2012.

Estimated nutritional needs for moderately malnourished children were also proposed in the 2011 Food Aid Quality Review Report to USAID by Tufts University (28), which based the required nutrient intake at approximately 115% of the Recommended Nutrient Intakes (RNIs) by FAO/WHO. The WHO's proposed nutrient composition for supplementary foods contains slightly higher amounts of most nutrients than the estimated nutritional needs proposed in the Food Aid Quality Review Report.

Fortified blended foods

The most frequently used specially formulated foods in SFPs are fortified blended foods. These products, typically consisting of CSB and wheat-soy blends (WSB), have been used for decades, with slight changes over the years. Reviews on the effectiveness of supplementary feeding programs, such as that by Navorro-Colorado et al. (29) in 2008, indicate that fortified blended foods have proven not to fully meet the nutritional needs of children with MAM. A 2008 review by Hoppe et al. (30) regarding the content of fortified blended foods attributes this to insufficient amounts of certain nutrients, large antinutrient contents (such as dietary fiber and phytates), low energy density, a bulky nature, low essential fatty acids, and no milk or animal-sourced proteins. The main buyers of fortified blended foods—the World Food Programme (WFP), the United Nations Children's Fund (UNICEF), and the United States Agency for International Development (USAID)—have more recently taken action to improve the quality of such foods. WFP adapted a CSB to include skimmed-milk powder, increase sugar for higher energy density, and improve oil content to optimize shelf-life. This product, called Supercereal-Plus, was found to be effective in treating children with MAM in a Malawian study by LaGrone et al. (31) in 2012. USAID has also updated several products based on recommendations made by Tufts University in the 2011 Food Aid Quality Review (28) to upgrade micronutrient specifications, increase energy and fat content, include animal-sourced protein, and improve the size of packaging.

Ready-to-use products

Although originally designed for the treatment of children with SAM, RUTF is considered appropriate and has proven effective in the treatment of MAM children, as shown by effectiveness studies in Niger in 2007 by Defourny et al. (32) and in Malawi in 2005 by Patel et al. (33). Simplified protocols have been developed within CMAM programs that provide RUTF to both SAM and MAM children, rather than providing separate products for each condition (34). A recent study in 2015 by Maust et al. (35) in Malawi demonstrated this integrated approach improved recovery rates and increased program coverage compared to the standard therapy consisting of RUTF for SAM children and fortified blended food for MAM children. However, as expressed in a recent policy brief by Action Contre la Faim International (36), not all agencies embrace this integrated approach due to concerns that the use of RUTF for MAM treatment may interrupt the supply of RUTF for children who need it most (i.e. children suffering from SAM).

Other ready-to-use products have been developed based on the original RUTF formulas but adapted specifically for MAM treatment. These products, called ready-to-use supplementary foods (RUSF), are to be used in addition to an improved home diet. Example products include: 1) Plumpy'sup™, produced by Nutriset in France, with ingredients similar to RUTF except skimmed-milk powder is replaced by whey and soy protein isolates; 2) Soy-based RUSF, produced by Project Peanut Butter in Malawi, which contains soybeans, soybean oil, peanut paste, sugar, and micronutrients; and 3) Indian Ready-to-Use Food for Children (RUFC), produced by WFP in India, which contains chickpeas, rice flour, oil, and a lower amount of skimmed-milk powder (10% of the total food weight compared to 30% in of the weight in RUTF).

According to a 2013 Cochrane review by Lazzerini et al. (37), RUTF and RUSFs have led to faster recovery rates and improved MUAC and WHZ when compared to fortified blended foods in MAM treatment. A study in Malawi by Wang et al. (38) examined the acceptability and feeding practices associated with different supplementary food items and found that ready-to-use products are less likely to be shared with other family members than fortified blended foods. Yet due to higher cost, distributing RUTF or RUSFs is less common than distributing fortified blended foods. According to a review by de Pee and Bloem in 2009 (39) of specially formulated foods for the management of MAM, an estimated 50,000 MAM children are treated using ready-to-use products compared to approximately 2 million MAM children treated with fortified blended foods worldwide each year.

Remaining questions regarding what can be done to improve and sustain recovery from MAM

A recent review of the evidence supporting current practices for treating MAM by Webb (40) in 2015 highlights the need for more clinical trials to be conducted on effective programmatic approaches for managing MAM. This message is repeated in other systematic reviews, such as Lenters et al. (41) in 2013, as well as conclusions from expert panels, such as the 2012 WHO consultation on MAM (20). Furthermore, Webb (40) points out the desire for policy makers to obtain more evidence specifically regarding the cost-effectiveness of interventions. These requests are driven by the fact that too few high quality studies have been conducted on the effectiveness and cost-effectiveness of MAM treatment in order to produce a large, rigorous body of empirical evidence upon which global standards can be developed. This lack of evidence-based consensus around programmatic standards is apparent by the diverse practices and approaches being implemented around the world (that often do not adhere to recommended principles previously described in Table 3) with subsequently inconsistent effectiveness.

Does evidence support the inclusion of whey protein in supplementary foods?

Many of the traditional formulas for fortified blended foods do not include any animal-sourced protein. Recommendations by Tufts University to USAID in the Food Aid Quality Review (28) include the addition of 3 g of whey protein concentrate per 100 g of dry fortified blended food. Yet a recent review in 2014 by Noriega and Lindshield (42) argues that the evidence behind such a recommendation is weak, given the lack of studies specifically comparing different isocaloric and isonitrogenous supplementary foods in the treatment of MAM.

Overall, the quality and quantity of protein are known to be important for growth in young children, and studies have suggested that animal-sourced protein improves nutritional outcomes in undernourished populations. A 1992 study in Mexico by Allen et al. (43) and a 1990 study in Jamaica by Walker et al. (44), both showed greater weight gain and linear growth were correlated with higher intakes of milk in toddlers. An additional study by Walker et al. (45) on Peruvian toddlers in 1997 confirmed these findings by showing that consumption of animal-sourced protein was associated with increased linear growth in toddlers whose food intake (complementary to breast milk) was low. In 2003, Grillenberger et al. (46) found that supplementation with animal-sourced protein increased lean body mass in Kenyan children in comparison with those who received a non-animal-sourced energy supplement or no supplement at all. A prospective cohort study by Stein et al. (47) in 2003 followed Guatemalan women who received dried skimmed milk supplements in childhood and found they were more likely to be taller as adults than those who received a non-animal-sourced protein supplement. Delchevalerie et al. (48) in Sierra Leone found similar recovery rates among moderately malnourished children treated with an RUSF containing whey compared to a fortified blended food that contained no animal-sourced protein; however the RUSF was associated with shorter treatment time and lower transfer rate to inpatient care. Ackatia-Armah et al. (49) in Malawi found recovery rates to be higher among children who received treatment foods containing animal-sourced protein (73% for whey-containing RUSF and 68% for CSB++ containing dried skimmed milk) than children receiving one of two types of fortified cereal blends with no animal-sourced protein (at 61% and 58%). Also, Karakochuk et al. (50) showed recovery rates of moderately malnourished children in Ethiopia were higher among those receiving a whey-containing RUSF (73%) than those receiving CSB with no animal-sourced protein (67%). While these studies demonstrate positive effects of consuming animal-sourced protein, they do not allow for the determination of whether improved outcomes were due to the animal-sourced protein or the total protein, total energy intake, and other factors that differed between the study food and the comparison food.

More recently, some intervention trials have investigated more comparable treatment foods that better isolate the effect of whey and other dairy protein in the treatment of wasting. When treating children for SAM, a study by Oakley et al. (51) in Malawi found that substituting soy protein for dried skimmed milk in RUTF (lowering the milk content to only 10% of the total food weight) resulted in lower recovery rates and poorer growth outcomes than children who received RUTF with 25% milk. However, another Malawian study by Bahwere et al. (52) in 2014 substituted whey protein for dried skimmed milk in an RUTF for the treatment of SAM and observed similar recovery rates across both groups of children receiving either the milk-based RUTF or the whey-based RUTF. This study provides strong evidence towards the effectiveness of using whey in therapeutic foods for treating children with SAM; but the question remains whether similar results would be seen in MAM children.

Matilskey et al. (53) compared two isonitrogenous RUSFs, one containing soy and the other containing dried skimmed milk, with a CSB that contained no animal-sourced protein in the treatment of moderately acutely malnourished children in Malawi. The two RUSFs resulted in higher weight gain, MUAC gain, and recovery rates than the CSB; however, no differences were seen between children receiving the soy RUSF versus the milk RUSFs. A clinical trial by LaGrone et al. (31) in Malawi found that including some whey in an RUSF (to create a combined whey/soy based RUSF) for MAM treatment did not increase recovery rates when compared to a soy-only RUSF.

These studies show that the inclusion of whey in the treatment of MAM may improve lean mass accumulation, but no improvements on linear growth or initial recovery rates have been proven. The lack of effect on linear growth may be, in part, due to the fact that only one of the two factions in milk—casein, not whey—stimulates production of insulin-like growth factor-1 (IGF-1), as shown by Hoppe et al. (54) in a 7-day trail supplementing school-aged boys with casein or whey.

Nonetheless, according to a 2004 review of therapeutic applications of whey protein by Marshall (55), whey has been linked to many other biological benefits, including muscle restoration, immune function, and intestinal integrity, in animal studies. For example, in a 2007 study by Bjornvad et al. (56) comparing whey and soy protein supplementation in piglets, whey led to increased body and small intestinal weight as well as stimulated soft tissue growth (internal organs, muscle and fat). A review of whey in fortified blended foods for vulnerable groups by Hoppe et al. (30) in 2008 shows that adding whey in fortified blended foods would improve the overall protein quality of MAM treatment foods, which could have potential metabolic advantages. Whey protein is an excellent source for branched-chain amino acids, which are metabolized by muscle and counteract lean tissue breakdown—a critical step in the recovery from acute malnutrition. Also, the authors of the review (30) conclude that bioactive factors in whey, such as α-lactalbumin, β-lactoglobulin, serum proteins, lactoferrin, and immunoglobulins, might have beneficial effects on malnourished children. These compounds have important biological functions related to growth and immune system support, such as iron binding, tissue repair, and resistance to infections; however, data from clinical trials with children with malnutrition are lacking. Therefore, the use of whey in supplementary foods to optimize and sustain recovery from MAM needs further clarification from future studies, including cost-effectiveness analyses given the additional cost of whey protein over non-animal-sourced protein.

Does the type of food provided in SFP affect post-discharge outcomes?

A 2010 study by Nackers et al. (9) in Niger compared outcomes at 6 months after discharge from an SFP where children received either RUTF or CSB during treatment. Results showed no significant differences in relapse, morality, lost to follow-up or linear growth rates between children who received RUTF and those who received CSB. A second study, by Chang et al. (10), followed children for 12 months after treatment for MAM with either CSB++, a soy/whey RUSF, or a soy-only RUSF. Although all three foods led to similar initial recovery rates, the soy/whey RUSF resulted in a higher proportion of children sustaining recovery over the subsequent year (67% for soy/whey RUSF versus 62% for CSB++ and 59% for soy RUSF; $P = 0.01$). Although conclusions from the Nackers et al. (9) study in Niger and the Change et al. (10) study in Malawi are not consistent, differences may be attributed to several factors, including: 1) different definitions of MAM and relapse as Nackers et al. defined MAM using weight-for-height between 70% and < 80% of the NCHS median while Chang et al. used the 2006 WHO standards of WHZ (< -2 and ≥ -3 WHZ); 2) Nackers et al. presented results at 6 months after discharge while Chang et al. examined a full year of follow-up; and 3) differences in environmental factors, cultural dietary habits, and the overall setting. Future studies are needed that clarify how the type of supplementary food provided during MAM treatment affects post-discharge relapse, mortality, illness, and linear growth.

What are the best admission and discharge criteria to indicate full recovery and prevent relapse?

Debate continues regarding the most appropriate admission and discharge criteria for MAM treatment programs. Traditionally, children with SAM and MAM have been admitted and discharged based solely on WHZ, yet accumulating evidence continues to show MUAC to be a better predictor of mortality than WHZ, thus a better means of identifying the most at-risk children. In 2007, MUAC was endorsed by WHO and other international agencies for use in active case finding, referral, and admission into CMAM programs (57). In 2012, a study by Briend et al. (58) in Senegal demonstrated that MUAC alone had the highest receiver operating characteristic (ROC) curve when compared to WHZ alone and WHZ plus MUAC, indicating MUAC alone to be the best at identifying high-risk children. Furthermore, a study by Goossens et al. (59) in Burkina Faso confirmed MUAC to be a useful admission and discharge criterion in therapeutic feeding programs for SAM. In a 2015 study by Binns et al. (60), MUAC was shown to be appropriate for monitoring children's progress throughout treatment in three country contexts (Malawi, Ethiopia and Bangladesh). In a separate study, Binns et al. (61) proved using MUAC $\geq$ 125 mm for two consecutive visits to be a safe and practicable discharge criterion in the treatment of acute malnutrition. Measuring MUAC may even be appropriate for caregivers to monitor children's nutritional status for better early detection, as shown by Ale et al. (62) in rural Niger.

While these findings support the use of MUAC over WHZ to determine anthropometric recovery from MAM, little is known regarding its impact on sustaining recovery for longer periods of time and what effect different cut-offs have on relapse rates. For example, an observational study by Trehan et al. (63), found that higher

MUAC and WHZ upon SFP discharge were associated with sustaining recovery during the subsequent year following recovery. Authors suggest that increasing the recommended cut-offs for discharge may improve outcomes following initial recovery. As recommended in a 2010 consultation meeting by WHO and other international partners (20), more prospective clinical trials are needed to better understand the relationship between SFP admission and discharge criteria and relapse following MAM recovery.

Furthermore, questions remain regarding the functional implications of using MUAC as a sole discharge criterion. While MUAC is well known to be a better predictor of survival than WFH, less is understood about MUAC's ability to estimate body composition, particularly the proportion of muscle mass to lean body mass, which plays a key role in a child's susceptibility to becoming acutely malnourished. Studies by Heymsfield et al. (64) in 1982, Briend et al. (65) in 1989, and Van den Broeck et al. (66) in 1998 demonstrate that muscle depletion is clinically associated with survival. In a more recent study by Jensen et al. (67) in 2012, authors suggest the key to resisting malnutrition is the capacity for muscle tissue to provide energy to other metabolically active organs, which is represented by the ratio of muscle mass to total lean body mass. In this study, researchers explored associations between MUAC and other anthropometric indicators with body composition in healthy, 3-year-old Danish children. Results showed that MUAC was highly correlated with muscle mass as a percentage of total lean body mass (0.489), and MUAC was more highly correlated with fat mass in relation to total body mass (0.571). These results confirm previous findings by Chomtho et al. (68) in 2006 that showed MUAC was a better predictor fat mass (explaining 63% and 72%

variability healthy and undernourished children, respectively) than total fat free body mass (explaining only 16% and 28% healthy and undernourished children, respectively). Also, Jensen et al. identified the best indicators for estimating the proportion of muscle mass to lean body mass include MUAC *and* subscapular skinfold; yet, this only explained 34% of the variance. While Chomtho et al. suggest the link between MUAC and muscle mass is stronger in malnourished children than healthy children, the limitations of MUAC in reflecting body composition, particularly with regards to muscle mass, should be taken into consideration when determining appropriate discharge criteria for SFPs.

Is measuring weight enough to determine full recovery from MAM?

Most children are deemed to have recovered from MAM once they reach a certain threshold MUAC or WHZ, ultimately representing a presumably healthy weight. However, Golden (26) highlights the importance of full recovery from acute malnutrition as something that goes beyond a temporary gain in weight, as he states: "Weight gain, of itself, does not indicate a return to physiological, biochemical, immunological, or anatomical normality". Given the known high relapse rates of children following discharge for MAM based solely on MUAC or WHZ, it is plausible that other biological factors may not have fully recovered, leaving children susceptible to poor post-discharge outcomes. The WHO 2012 technical consultation on supplementary foods for the management of MAM (25) recommend that future studies measure outcomes beyond weight gain, such as linear growth, in order to decipher if achieving weight gain alone is enough for a full and sustained recovery from MAM. As Golden (26) explains that rapid linear growth is possible in young children and linear growth may even be a better indicator of diet adequacy than weight gain. Also, Briend et al. (69) point to the need for linear growth alongside accumulated lean tissue mass in recovery from acute malnutrition.

In addition to linear growth, outcomes regarding immune function at the time of discharge need to be explored. Authors of the Chang et al. (10) study conclude that children remain at high risk for relapse following initial recovery from MAM possibly because of underlying immunological deficiencies that persist beyond anthropometric recovery. This hypothesis is supported by a 2016 study in Burkina Faso by Cichon et al. (37) that showed children with MAM have elevated immune markers (C-reactive protein (CRP) as well as α1-acid glycoprotein (AGP)), indicating inflammation in the body even without identified symptoms. These results suggest that underlying infections during MAM can go unaddressed due to latent symptoms. While a systematic review by Rytter et al. (8) in 2015 showed that more immune function parameters (such as white blood cells, acute phase proteins, complement proteins, lymphocytes, and antibody levels) seem to be affected in children with SAM than children with MAM, the authors point out that the number of scientific studies being carried out on immune deficiency in malnutrition is dwindling, despite modern knowledge of immunological methods. They conclude that our current understanding of immune function in malnutrition remains very limited, with most of the evidence based on outdated methodologies. A revived pursuit of rigorous research examining immune deficiency during and following MAM could facilitate enhanced treatment protocols that go beyond the promotion of short-term weight gain to include a reversal of underlying immunological deficiencies, ultimately improving the sustainability of recovery.

Can an SFP that combines curative and preventive approaches improve the sustainability of MAM recovery?

Given the high proportion of children who experience relapse to MAM, the development of SAM, illness, poor linear growth, and death after recovery from MAM, there may be need for curative programs to also incorporate preventive approaches at the end of treatment in order to prevent future relapse. One common approach to preventing acute malnutrition in at-risk populations includes distributing fortified blended foods or small quantity lipid-based nutrient supplements. Therefore, distributing such preventive products at the end of treatment to children who have been discharged from SFPs and remain at-risk for developing MAM again may help to reduce relapse, yet this remains untested. The Chang et al. (10) study following children after recovery from MAM in Malawi showed that the most relapses occurred during the time of year when malaria prevalence is highest. Therefore, it is plausible that services aimed to prevent malaria, such as the provision of a bed net and malaria chemoprophylaxis, provided to children following recovery from MAM may reduce the risk of relapse. Also, the provision of albendazole and zinc may also lower the risk of relapse by addressing underlying illness, as shown by Ryan et al. (70) in a trial that demonstrated the provision of zinc and albendazole attenuated the progression of environmental enteric dysfunction in Malawian children ages 1-3 years. Studies are needed to identify what effect these preventive interventions may have in reducing relapse among children who recovery from MAM.

Can links to non-nutrition specific interventions improve sustained recovery from MAM?

Momentum has been gaining around the need to implement multi-sectoral programming to address acute malnutrition. Examples include recent policies such as

USAID's Multi-Sectoral Nutrition Strategy 2014-2025 (71), the World Bank's Improving Nutrition through Multi-Sectoral Approaches (72), and UNICEF's Multi-sectoral Approaches to Nutrition: Nutrition-specific and nutrition-sensitive interventions to accelerate progress (73). However, little has been done to explore how nutrition-sensitive programs may reduce relapse following initial recovery from MAM.

A key step in determining if and which nutrition-sensitive interventions may reduce relapse is first identifying risk factors of relapse, including both at the individual child and household levels. Poor infant and young child feeding practices, unsanitary living conditions, food insecurity, poor dietary diversity, and low socioeconomic status have all been linked to acute malnutrition; these same factors may also be associated with relapse following initial recovery from acute malnutrition. It is plausible that returning to an unchanged household environment following recovery from MAM may contribute to relapse. Therefore, research that identifies household risk factors associated with relapse could have significant implications on how best to prevent relapse and improve the sustainability of recovery from MAM.

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Methods

Research Setting and Research Team

All research in this dissertation was conducted in southern Malawi between February 2013 and June 2016. Data were collected from children aged 6-62 months and their primary caregivers recruited through various rural health clinics. Malawi was ranked as the 18th least developed country in the world in the 2013 UNDP Human Development Report, with over half of its population living in poverty (1). As 85 percent of Malawi's population live in rural areas (1), children in this research setting almost universally come from poor, subsistence farming families where their staple crop, maize, is harvested following a single annual rainy season (2). Animal-sourced foods are rarely consumed and are estimated to contribute only 2-7% of the energy intake of infants in this population (3, 4). Acute malnutrition typically peaks each year from December to March, just prior to the harvest in April. More than 40% of Malawian children under 5 years old are stunted and the under-5 mortality rate is 6.8% (5).

Data collection was carried out by a team of Malawi nationals and expatriate staff under the St. Louis Nutrition Project from Washington University in St. Louis. Before each study began, the study team, including research nurses, drivers, program coordinators, and community health workers, were trained extensively on the study protocols. Much of the staff had worked on previous studies by Washington University in St. Louis and transitioned well into the new studies. The PhD candidate joined the study team in March 2014 and oversaw all data collection processes for the remainder of the research.

Ethical Approval

All studies were approved by the University of Malawi's College of Medicine Research and Ethics Committee, Washington University's Human Research Protection Office, and Tufts Medical Center and Tufts University Health Sciences Institutional Review Board. Permission to conduct the study was also obtained from local Malawian authorities including each District Health Officer and/or District Nutritionist where the studies were implemented. All caregivers of children who met enrollment criteria for the studies and sub-studies were asked to give verbal and written consent for participation in each study prior to their participation.

Data Entry and Anthropometrics

Data for all three studies were double-entered into Access (Microsoft Corp., Redmond WA) databases and compared to original paper charts to resolve any discrepancies. Anthropometric indices were based on the World Health Organization's 2006 Child Growth Standards (6) and calculated using the WHO Anthro software (WHO, Geneva). Implausible z-scores were defined by the WHO Growth Standards as HAZ < -6 and > 6, WAZ < -6 and > 5, and WHZ < -5 and > 5 (6).

Chapter 1 Methods

The first study consisted of a double-blinded, randomized controlled clinical effectiveness trial where we compare two RUSFs—a soy RUSF versus a whey RUSF—in the treatment of children with MAM.

Subjects

Children aged 6-59 months with MAM, as defined by a mid-upper-arm circumference (MUAC) of 11.5-12.4 cm without bipedal edema (7, 8), were recruited at 18 rural sites in southern Malawi from February 2013 to November 2014, including some sites in border areas serving children from Mozambique. MUAC was chosen as the anthropometric criterion for entry and exit in this study, in contrast to WHZ (4, 9-13), given the more recent evidence that MUAC is better suited for identifying those malnourished children at highest risk for mortality (14-17).

Study Design

The primary outcome was recovery from MAM, defined as achieving a MUAC of 12.5 cm without bipedal edema within 12 weeks of therapy. If children did not recover, they were categorized as having continued MAM, developing SAM (MUAC < 11.5 cm and/or bipedal edema), dying, or defaulting (failing to return for three consecutive visits). Secondary outcomes consisted of changes in MUAC, weight, and length; time to recovery; and any adverse events.

A minimum sample size of 1073 children in each group was sought to detect an improved recovery rate in the novel whey RUSF group of 88%, compared to an expected recovery rate of 84% in the soy RUSF group (4, 10, 11), assuming 95% sensitivity, 80% power, and an incomplete follow-up rate of 10% (18).

Random allocation was performed by caregivers drawing opaque envelopes that contained one of two coded papers corresponding to either whey RUSF or soy RUSF. This code was accessible only to the food distribution personnel, who do not assess participant outcomes, determine eligibility, or analyze data. The two RUSF formulations had similar color, taste, smell, and packaging. If there were two study participants from the same household, both children received the same type of food to reduce the likelihood of confusing the assigned interventions.

Study Foods

Both RUSFs were produced by Project Peanut Butter in Blantyre, Malawi (19) and underwent quality assurance and safety testing for aflatoxin and microbial contamination at the Malawi Bureau of Standards and Eurofins Scientific Inc., Des Moines, Iowa, USA. A combination of 4.9% WPC80 and 18.7% whey permeate (Arla Foods Ingredients Group P/S, Aarhus, Denmark) was used in the whey RUSF, along with peanut paste, sugar, palm oil, soy oil, emulsifier, and a customized micronutrient premix needed to meet the minimum World Health Organization (WHO) recommendations for supplementary foods (20). The soy RUSF recipe used has previously been shown effective in treating children with MAM (4, 10) and served as the control RUSF. This soy RUSF included extruded soy flour, peanut paste, sugar, palm oil, soy oil, a micronutrient premix, and dicalcium phosphate or calcium carbonate (Roche, Mumbai, India). The soy RUSF contained no animal-source proteins (See **Table 1 in Chapter 2**). In order to maintain blinding, the volume and weight of RUSF provided (on a per-kilogram basis) was the same between the two interventions, although this led to some differences in nutrient composition (See **Tables 2** and **3 in Chapter 2**).

Subject Participation

Children were evaluated for acute malnutrition by nutrition research assistants and senior pediatric research nurses, trained and supervised by the senior investigators. MUAC was measured with a standard insertion tape to the nearest 0.1 cm (TALC, Harpenden, UK). Weight was measured using an electronic scale to the nearest 5 g (Seca 334, Hamburg, Germany). Length was measured to the nearest 0.1 cm using a rigid length board (Seca 417, Hamburg, Germany). Children were also evaluated for kwashiorkor by assessing for bilateral pitting edema. The caregivers of children who met enrollment criteria were asked to give verbal and written consent for participation in the study prior to randomization. Children with chronic illnesses (not including HIV or TB), a known allergy to milk, soy, or peanuts, those who had received treatment for acute malnutrition in the previous three months, and those who were not permanent residents of the vicinity near the clinic site were excluded.

Once enrolled, each child's caregiver was interviewed regarding the child's demographic characteristics, appetite, infectious symptoms, and known food allergies. Each caregiver also completed the Household Food Insecurity Access Scale (HFIAS) (21) and a dairy-focused food frequency questionnaire (See Appendix 1).

A two-week supply of either soy RUSF or whey RUSF at a dose of approximately 75 kcal/kg/d was provided along with nutrition counseling and instructions for proper feeding of the RUSF. Therefore, the number of distributed food packets varied according to the weight of the child. Caretakers were instructed to feed the RUSF only to the enrolled child, to provide additional complementary foods, and to ration the allotted food to last until the next fortnightly distribution. If the child was a twin, twice the amount of food was given to the caregiver to feed both children in order to limit sharing between the twins and increase the likelihood that the enrolled child received the full ration intended.

Children were scheduled for follow-up appointments on a fortnightly basis. At each subsequent visit, anthropometric measurements were repeated and caretakers reported on the child's clinical symptoms. If the child remained moderately malnourished, additional RUSF was provided. Children that became severely malnourished during the course of the treatment were treated as outpatients with ready-to-use therapeutic food (RUTF) (22) or, if necessary, in an inpatient nutritional rehabilitation center. Children that missed appointments were sought by the research team in their homes and assessed there if needed.

Statistical Analyses

Rates of MUAC and length gain were calculated in mm/d over the duration of each participant's time in the study. Weight gain was calculated in g/kg/day for the duration of the study as well as from enrollment to the second follow-up visit (or first visit for those whom only one visit was recorded). Intention-to-treat analyses were used and all tests were two-sided. Bivariate analysis was conducted to compare characteristics between the two groups to ensure randomization was successful. Dichotomous variables were compared with either Fisher's exact test or the chi-squared test; the Student t-test was used for comparing continuous variables. P-values < 0.05 were considered to be statistically significant.

As conducted in a similar study comparing the effect of two different treatment foods on the recovery from MAM by LaGrone et al. (4), binary logistic regression and survival analyses was also performed. The binary logistic regression model was chosen to determine the impact of RUSF type on recovery while controlling for other factors. Backward elimination was used to created the model whereby all pre-determined covariates were initially included in the model but later removed if the P-value > 0.05. Initial covariates included: type of RUSF (whey vs. soy), sex, age, MUAC upon admission into the SFP, WHZ upon admission into SFP, if the child had a fever during the two weeks prior to admission into the SFP, if the child had diarrhea during the two weeks prior to admission into the SFP, seasonality (if the child was admitted to the SFP during harvest), if the mother was known to be HIV+, household food security (score on the Household Food Insecurity Access Scale (21)), and whether or not the child was breastfeeding. Survival analysis was conducted following methods proposed by Goel et al. (23) in order to compare the time to recovery between the group receiving whey RUSF and those receiving soy RUSF. The log-rank test was used to test whether the difference in time to recovery between two groups was statistically significant. All statistical analyses were performed in Stata Version 13.0 (StataCorp LP, College Station, TX).

Cost-Effectiveness Analysis

This analysis aimed to assess the marginal cost effectiveness of treating children with whey RUSF in comparison to soy RUSF following methods proposed by Puett et al. (24). Total costs included in the analysis consisted of food production costs and operational costs for providing MAM treatment through a SFP. This analysis did not include costs of participating households, as is recommended by the Panel on Cost-Effectiveness in Health and Medicine of the US Public Health Service (25), due to the analysis being conducted after the clinical trial was completed, so that contacting previous participants was not feasible. However, it is not likely that household level costs varied significantly between the two types of treatment (whey vs. soy RUSF), given that patient participation was identical in both groups. Cost data were paired with outcome (effectiveness) data collected during the clinical trial, in order to produce cost-effectiveness ratios. The two cost-effectiveness ratios generated from the analysis were: 1) the cost of each food product per outcome (child recovered) and, 2) the cost of each food product *and* SFP operations per outcome (child recovered).

Data collection was divided among the cost of food production and the cost of implementing MAM treatment in an SFP. The costs associated with food production included raw materials, shipping and transportation, import and duty taxes, packaging, factory operations, and product testing. Production amounts were also verified in order to calculate a cost per kg of finish product. This information was collected via interviews with the factory and production managers at Project Peanut Butter, where the food products were produced. When possible, costs quoted by individuals were verified by invoices, expense reports, and other financial record keeping documents. Suppliers were contacted for pricing of raw materials and packaging. The international shipping company, Starship International, used by production factory was contacted to collect shipping costs of imported materials into Malawi. The food-testing laboratory, Silliker Labs, was contacted to collect costs associated with product quality testing. All prices gathered were in 2015 USD and all Malawian Kwacha (MKW) were converted to 2015 USD (as 1 MWK = 0.00183 USD according to Online Currency Converter: Oanda.com, rate as of 20 Aug 2015). Costs were summed and multiplied by the appropriate ratio to create a total cost per kg of finished product for both soy and whey RUSFs.

In order to collect all costs associated with implementing MAM treatment through an SFP, interviews were held with the Office Manager, Program Manager, and Scientific Administrator at St. Louis Nutrition Project as well as the Data Analyst at Washington University, School of Medicine. When total costs were not exclusive to the implementation of the SFP, but rather included additional activities (such as research activities or treatment for SAM children), an estimated percent cost allocated exclusively to SFP operations was used. These estimated percents were based on direct observations while working with St. Louis Nutrition Project as well as interviews with the Program Manager and clinic staff[1]. Costs were summed and divided by the total number of children treated in the SFP to generate a total SFP operational cost per child treated. This was added to food costs to produce the final cost-effectiveness ratios: a total cost (including food and SFP operations) per child treated and total cost (including food and SFP operations) per child recovered (that is, cost per child adjusted for the percent recovered). For more details regarding the cost-effectiveness calculations, see Addendum 2 to Chapter 1.

[1] Using more precise methods such as timed observations, spatial measurements, etc. would likely have produced more accurate % costs; however, this analysis was conducted after the study had completed. Therefore, estimations were used. Still, these estimations were discussed and refined based on discussions with several staff from St. Louis Nutrition Project.

Chapter 2 Methods

In the study presented in Chapter 2, we assess whether a package of simple and affordable health and nutrition interventions added after achieving anthropometric criterion for nutritional recovery from MAM could improve the proportion of children who sustained recovery for one year following treatment.

Subjects

Children aged 6-62 months who had recovered from MAM, as defined by a mid-upper-arm circumference (MUAC) ≥ 12.5 cm without bipedal edema (8), were recruited from 21 rural SFP clinics in southern Malawi from April 2014 to June 2015. Children were excluded if they had a chronic debilitating illness, or had a history of peanut, milk, or soy allergy. Children were also excluded if they had received therapy for acute malnutrition within one month prior to admission into the SFP, in order to focus on the sustained recovery from an initial discrete episode of MAM. Those whose MUAC dropped below 11.5 cm or who developed edema during initial treatment for MAM were also excluded from the study, as they were considered to have progressed to SAM and were treated as such.

Study Design

The study was a cluster randomized, controlled clinical effectiveness trial. Randomization was performed across clinic sites, rather than at the individual level to minimize the risk of sharing and cross contamination. The primary outcome was the proportion of children who sustained recovery, defined as maintaining MUAC ≥ 12.5 cm without bipedal edema, at each follow-up visit across 12 months following initial recovery from MAM.

Before enrolling in the study, all children were diagnosed with MAM, defined as having MUAC 11.5-12.4 cm without bipedal edema and enrolled into an SFP program. During this initial SFP treatment, children consistently received one type of the following foods: a whey-based RUSF, a soy-based RUSF, or RUTF all dosed at approximately 75 kcal/kg of body weight/day.[2] Therefore, the number of food packets distributed to each child varied according to weight. Caregivers were instructed how to properly feed the food to the malnourished child, not to share or sell the food, and to ration the food until the next distribution. Children returned on a fortnightly basis where anthropometrics were repeated and children were reassessed for clinical symptoms of illness. If the child remained moderately malnourished, an additional two-week ration of food was provided. Children who became severely malnourished were transferred to an outpatient therapeutic program (OTP) or inpatient center where they were treated according to the Malawian national guidelines. If a child remained moderately malnourished after 12 weeks of SFP treatment, the child was referred to an OTP or hospital for further assessment and treatment as necessary. Children were defined as "recovered" from MAM if they had a MUAC $\geq$ 12.5 cm without bipedal edema. Upon discharge (which was also the time of enrollment into this follow-up study), all caregivers received nutrition counseling. These SFP treatment protocols were the same across all clinics, regardless of whether or not the site was allocated to receive the intervention.

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[2] The type of food provided was based on availability of ingredients for local RUSF or RUTF production in Malawi. Type of food received during initial SFP treatment was accounted for during analysis.

Participants and field researchers were not blinded to the allocation of groups, as it was inherently evident whether or not children received the package of interventions. However, after each child's anthropometric and clinical data were entered into the computer database, the group allocation was blinded during statistical analyses.

When calculating sample size, a correction factor was used to adjust for any implementation or populations differences among sites. An intracluster correlation coefficient (ICC) of 0.007 and a coefficient of variation of cluster size of 0.65 were calculated from pilot data and similar studies conducted previously at similar study sites (9, 12). A power of 80% and alpha of 0.05 were used to identify a sample size sufficient to detect a 10-percentage point difference in the proportion of children that sustained recovery between the control and intervention groups. Estimating that 63% of children would sustain recovery for 12 months without any additional interventions (9), a minimum average of 58 participants per cluster was calculated to be necessary across the 21 clusters. Sample size was calculated using Stata Version 13.0 (StataCorp LP, College Station, TX). An additional 279 children were enrolled to account for the possibility of a high lost to follow-up rate.

To identify if an association existed between immune function and sustained recovery following treatment for MAM, serum complement C3 (as a proxy for immune recovery (26)) was measured in a random sample of 145 children at the time of SFP discharge and four weeks later. Whole blood was drawn into a heparinized tube and placed in an insulated plastic box with cold packs in the field. Immediately upon returning from field clinics, the blood was centrifuged to isolate the plasma, which was frozen at -80°C. Samples were transferred while frozen to the Core Laboratory at St.

Louis Children's Hospital for analysis of serum complement C3 levels (Roche Cobas, Indianapolis, IN).

Intervention

The control group received nutrition counseling at the point of discharge from an SFP, consisting of messages regarding proper complementary feeding, caretaker recognition of common childhood illnesses, and appropriate health-seeking behaviors. The treatment group received the same counseling plus five additional components that made up the intervention package:

1. 40 g/d of a lipid-based nutrient supplement (LNS) providing 200 kcal and one Recommended Dietary Allowance (RDA) of almost all micronutrients for 8 weeks upon discharge from SFP (See **Table 1 in Chapter 2**). The LNS consisted of 28% peanut paste, 18% non-fat dry skimmed milk powder, 24.5% palm oil, 21.2% sugar, 6.8% custom micronutrient mix, and 1.5% emulsifier. The LNS used in this study was produced locally by Project Peanut Butter in Blantyre, Malawi and contained peanut paste, sugar, non-fat dry milk, palm oil, a premix containing concentrated minerals and vitamins, and an emulsifier. The product underwent quality assurance and safety testing for aflatoxin and microbial contamination at the Malawi Bureau of Standards and Eurofins Scientific Inc. (Des Moines, Iowa).
2. A single dose of albendazole (200 mg for < 2 years old and 400 mg for ≥ 2 years old) for deworming at the time of discharge from SFP. Administration of albendazole is common practice for deworming in developing countries and is part of many Community Management of Acute Malnutrition (CMAM) protocols.

3. 14-day course of 20 mg zinc sulfate starting at the time of discharge from SFP. The dose used here is the same as recommended after an episode of diarrhea and has also been shown to decrease the progression of environmental enteric dysfunction (27).
4. A single insecticide-treated bed net at the time of SFP discharge to reduce the risk of malaria.
5. Sulfadoxine-pyrimethamine for malaria chemoprophylaxis at a dose of approximately 25 mg/kg (sulfadoxine component) monthly during the peak of the rainy season (December-February), as most adverse outcomes in children who recover from MAM occur during this time (9). Sulfadoxine-pyrimethamine was chosen as the malaria prophylaxis due to its proven effectiveness (28), low cost, and local availability in Malawi.

These interventions have all individually been proven safe, effective, and affordable in this context to improve the overall health of children, but are often not universally implemented due to resource and logistical limitations. The package was thus provided specifically to this high-risk population to increase the likelihood of sustaining recovery, especially during the first few months after discharge from SFP and throughout the rainy season when malaria is more common.

Subject Participation

Information on demographic characteristics, health history, and household food insecurity was collected. Health history questions included caregiver-observed illness symptoms during the prior two weeks, immunization status, use of any nutritional supplements, use of malaria prophylaxis, timing of most recent deworming, and use of a bed net. Household food security was assessed using HFIAS (21). At enrollment and each subsequent visit, nutrition researchers and senior pediatric nurses conducted standard anthropometric measurements and assessed other clinical signs. Weight was measured using an electronic scale to the nearest 5 g; length was measured using a rigid length board to the nearest 0.1 cm; and MUAC measured with a standard insertion tape to the nearest 0.1 cm. Edematous malnutrition (kwashiorkor) was assessed by examining for bilateral pitting edema (See Appendix 2).

All caregivers were asked to return to the clinic for subsequent follow-up visits at 1, 3, 6, and 12 months after enrollment. Additional monthly visits were scheduled for all children during the height of the rainy season (December to February), where malaria prophylaxis was also provided at the intervention sites. Caregivers were also educated that they could bring their children for additional evaluations at any time during the course of the follow-up study if they were concerned about their child's nutritional status or if a community health worker had referred them.

Due to long periods of time (up to six months) between scheduled follow-up visits in which participants were expected to return to the clinic for re-assessment and data collection, a large proportion of participants being lost to follow-up was a concern for researchers. In order to address this issue, a caregiver who missed a scheduled follow-up appointment was visited by a community healthcare worker (CHW) at her home to remind her of her appointment and encourage her to return to the clinic the following fortnight. If the child failed to return, a second CHW was sent to the home. If the child missed three consecutive visits, the research team then traveled to the home in an effort to find the child and collect the necessary data. If the team was still not successful in locating the child, it was determined that the child was not reachable and considered to be defaulted from that scheduled follow-up appointment.

At the end of the 12-month follow-up period, each child was classified as having "sustained recovery," defined as having MUAC ≥ 12.5 cm at every follow-up visit for 12 months; "relapsed to MAM," defined as MUAC of 11.5-12.4 cm at any point during the follow-up period; "developed SAM," defined as MUAC < 11.5 cm and/or bipedal edema (kwashiorkor) at any point during the follow-up period; "died"; or "lost to follow-up (LTFU)," defined as defaulting on a scheduled visit and never returning. Poor outcomes included relapsing to MAM, developing SAM, death, or LTFU. If a child experienced two or more poor outcomes over the course of the follow-up period, the most severe category was assigned as the final outcome.

Statistical Analyses

Exploratory analysis was conducted using box plots and scatter plots to detect outliers. Implausible values were verified and corrected or else removed from the data set. Rates of MUAC and length gain were calculated in mm/d and weight gain was calculated in g/kg/day.

Bivariate analysis was conducted to compare enrollment characteristics between the control and intervention groups to ensure randomization was successful. Dichotomous variables were compared using chi-squared test, while the Student t-test was used for comparing continuous variables. P-values < 0.05 were considered statistically significant and all tests accounted for clustering at the clinic level. Similar analyses were carried out to compare characteristics between those who were LTFU and all others to ensure no significant differences existed between participants who completed the study and those that did not. Outcomes at each of the follow-up time points—1, 3, 6, and 12 months follow-ups—were first compared using bivariate analyses while including LTFU participants and then also compared using bivariate analyses while excluding LTFU participants. Given the seasonally high malnutrition prevalence (2) and relapse rates (9) during the malaria/rainy season (December-February), outcomes were compared specifically within this time of the year. Bivariate analysis was also used to compare characteristics between several different groups according to outcome, including: those who sustained recovery vs. all others; those who developed SAM vs. those who relapsed to MAM; those who died vs. those who survived; and those who relapsed to MAM once vs. those who relapsed to MAM multiple times.

Binary logistic regression models with cluster adjusted robust standard errors were used to determine if the intervention had a statistically significant impact on sustained recovery and identify other clinical factors predictive of sustained recovery. This method was chosen to align with analysis methods used in a similar follow-up study comparing the impact of two different types of MAM treatment on sustained recovery (12). A separate model was constructed for each follow-up time point (1, 3, 6, and 12 months) using backward elimination, whereby all predetermined covariates were initially included and dropped if they were not statistically significant at $P < 0.05$. Variables included in the initial models included: whether the child received the intervention; sex; age at the start of SFP treatment; type of food received; MUAC upon SFP admission; WHZ upon SFP admission; HAZ upon SFP admission; whether the child experienced fever during the two weeks prior to SFP admission; whether the child experienced diarrhea during the two weeks prior to SFP admission; seasonality (whether the child was admitted to the SFP during the harvest season; food security (score from the Household Food Insecurity Access Scale (21)); weight change during SFP treatment; days to recovery during SFP treatment; whether the mother was known to be HIV+; whether the child received malaria prophylaxis (other than that which was provided by the intervention); whether the child was dewormed in the month prior to enrollment; and whether the child regularly received supplements (including micronutrient supplements or specially formulated food supplements other than those provided by the intervention). All statistical analyses were conducted using Stata Version 13.0 (StataCorp LP, College Station, TX).

Chapter 3 Methods

The study presented in Chapter 3 consists of a sub-study that aimed to identify household-level factors associated with sustained recovery following discharge from an SFP.

Subjects and Study Design

This study consisted of an in-depth household (HH) survey administered prospectively, at the time of SFP discharge, to a randomly selected sub-sample of participants within a larger cluster randomized controlled trial (cRCT) examining relapse following MAM recovery. Complete methods of the larger cRCT have been described above in Chapter 2 Methods. Enrollment criteria into this sub-study were consistent with that of the larger cRCT. However, the HH survey was only conducted among children who did not receive an intervention. Outcome data were derived from the complete cRCT data set.

Subject Participation

Children were enrolled in the study at the time of recovery from MAM and subsequent discharge from an SFP. Informed consent was obtained from all caregivers. Upon enrollment, participants in the study scheduled an appointment for a data collector to travel to the caregiver's home within one week of the child's discharge from SFP. The survey was administered at the home of the caregiver by a trained data collector, either a senior pediatric research nurse or a community health worker. Information consisted of socio-demographic characteristics, child dietary diversity, infant and young child feeding practices, and water hygiene and sanitation factors that have been shown to be associated with child health and nutrition outcomes. Caregivers were also asked about their perceptions on the SFP, MAM, and relapse (See Appendix 3). The interview lasted approximately one hour.

Caregivers were asked to return to the clinic for subsequent follow-up visits at 1, 3, 6, and 12 months after enrollment to reassess the child's nutrition status and clinical signs of illness, including diarrhea and fever. Household food security was also assessed at each follow-up visit using the validated, nine-item Household Food Insecurity Access Scale (HFIAS) (21).

At the end of the 12 month follow-up period, each child was classified as having "sustained recovery", defined as having MUAC ≥ 12.5 cm at every follow-up visit for 12 months; "relapsed to MAM", defined as MUAC < 12.5 cm and ≥ 11.5 cm at any point during the follow-up period; "developed SAM", defined as MUAC < 11.5 cm and/or bipedal edema (kwashiorkor) at any point during the follow-up period; "died"; or "lost to follow-up," defined as defaulting on a scheduled visit and never returning. Poor outcomes were considered to be relapsing to MAM, developing SAM, lost to follow-up, or death. If a child experienced two such outcomes over the course of the follow-up period, the more severe category was assigned as the final outcome.

Household Survey

Data collected from the HH survey consisted of information pertaining to: 1) socioeconomic status (SES), 2) infant and young child feeding (IYCF) practices, 3) household food insecurity, 4) water, sanitation, and hygiene (WASH), and 5) maternal perceptions of MAM and relapse following MAM recovery.

SES. In order to measure SES, we collected indicators based on a recently validated SES index by Psaki et al. (29) in an eight-country study. This index, called the WAMI index, which stands for: water and sanitation, assets, maternal education, and household income. WAMI was chosen due to its simplified nature and associations with child HAZ (29). However, in the present study, monthly household income was not collected (as it is in the WAMI) due to many of the families in this context having informal sources of income and fluctuating monthly income (30). To account for this deviation, we collected information on additional assets and livestock ownership to help distinguish different levels of wealth within the local context (See Appendix 3). **Table 1** contains information on the definition and scoring of each indicator relating to SES.

Table 1.
SES indicators from the HH survey[1]

Indicator	Definition	Range
Maternal education	Number of years of completed education, ranging from no education up to "Form 4", the completion of primary and secondary education in Malawi. This equals 12 years of education. No respondents completed any higher education beyond Form 4.	0-12
Number of assets owned	Number of assets owned by anyone in the home. These include a mattress, bicycle, chair or bench, radio, mobile phone, flashlight, cabinet, pair of shoes, candle, lantern, and bank account.	0-11
Number of rooms in house	Number of separate rooms in a house. The term “separate” was defined as a physical wall, which did not include sheets or curtains dividing a space. The minimum and maximum number of rooms reported was 1 and 6, respectively.	1-6
Ownership of livestock	If anyone in the home owned any livestock. These include chickens, goats, cattle, dogs, pigs, or guinea fowl. This was considered an asset rather than a separate livelihood given the fact that all participants are agriculturists and the ownership of animals would be an additional indication of wealth.	0, 1

[1] HH, household

IYCF Practices. Indicators included in the HH survey regarding IYCF practices were based on the Food and Nutrition Technical Assistance's (31) guidance on Infant and Young Child Feeding Practices Definitions (32) and Measurements (33) as well as research by Ruel and Menon (34) in Latin America, Khatoon et al. (35) in Bangladesh, Ma et al. (36) in China, and Sawadogo et al. (37) in Burkina Faso who all measured IYCF practices and their associations with malnutrition. Modeled after these recommendations and previous studies, indicators collected in this study related to: 1) breastfeeding practices, 2) the introduction of complementary foods, 3) minimum meal frequency, and 4) minimum dietary diversity. Because recommended feeding practices vary according to age (32-34), the definition of indicators for breastfeeding and minimum meal frequency differed according to the age of the child. FANTA's technical guidance on IYCF practices recommends that children continue breastfeeding for the first 24 months of life (32). Therefore, for children under 24 months, the breastfeeding indicator is defined as whether the child was currently breastfeeding at the time of SFP discharge. For children over 24 months, the breastfeeding indicator is defined as or whether the child continued to breastfeed until the age of 24 months. Also, modeled after Ruel and Menon (34), minimum meal frequency was considered to be 2 or more meals for children age 6 to < 9 months, 3 or more meals for children ages 9 to < 12 months, and 4 or more meals for children ages 12 months and older. This ensured that the indicators were age appropriate. A 24-hour dietary recall was administered in order to calculate the minimum dietary diversity and minimum meal frequency indicators. **Table 2** contains information on the definition and scoring of each indicator regarding IYCF practices.

Table 2.
IYCF indicators from the HH survey[1]

Indicator	Definition	Range
Continued Breastfeeding	Continued breastfeeding until at least 24 months is recommended (32, 33). Therefore, in this indicator if the child was below 24 months or younger, they received a score of 1 if they were currently breastfeeding and 0 if they were not. For children over 24 months, they received a 1 if the age in which they stopped breastfeeding was beyond 24 months and 0 if it was prior to 24 months.	0,1
Introduction of complementary foods	If the solids and semi-solid foods were introduced to the child between 6-8 months. Participants received a score of 1 if solid and semi-solid foods were introduced between 6 and 8 months of age and 0 if food was introduced below 6 months or older than 8 months.	0,1
Minimum dietary diversity	Dietary diversity was based on 24-hour dietary recall emphasizing seven different food groups. Scores were assigned based on the number of food groups consumed. Food groups included grains, legumes, meats, eggs, vitamin A rich fruits and vegetables, other fruits and vegetables, and dairy products. The recommended minimum number of groups is 4 (32, 33). Participants received 1 if they consumed 4 or more food groups and 0 if they consumed less than 4 food groups in the past 24 hours.	0,1
Minimum meal frequency	Meal frequency was based on the previous 24 hours, including meals and snacks other than liquids. Minimum meal frequency was considered to be 2 or more meals for children age 6 to < 9 months, 3 or more meals for children ages 9 to < 12 months, and 4 or more meals for children ages 12 months and older (34). Participants received a 1 if the child received the minimum meal frequency in the previous 24 hours and a 0 if the child did not.	0,1

[1] HH, household; IYCF, Infant and young child feeding practices

Food Security. Household food security was assessed using the validated, nine-item Household Food Insecurity Access Scale (HFIAS) (21). Each respondent was asked a series of nine questions regarding the food security situation at the household level. Topics included: worrying about food, being unable to eat preferred foods, eating only a few kinds of foods, eating foods they did not want to eat, eating smaller meals, eating fewer meals, lack of food in the house, going to sleep hungry, and going a day without eating. If respondents answered “no” they were given a score of 0. If respondents answered “yes”, they were then asked to clarify how frequently this occurred in the last month. Respondents were given a score of 1 for rarely, 2 for sometimes, and 3 for often. Scores were summed and ranged from 0 to 27. This HFIAS was administered to the caregiver at the time of admission into SFP as well as 1, 3, 6, and 12 months following SFP discharge. Scores from all time points throughout the year were averaged. Food security can and often does change throughout the year between times when food availability is higher, during post harvest, and times when food is scarcer prior to harvest. Our data confirmed this as changes in participants’ HFIAS scores between follow-up visits ranged from 0 to 23 and averaged a 10-point difference between the lowest and highest HFIAS scores. Therefore, an average over the course of the year was chosen to help account for these fluctuations.

WASH. Indicators used to capture WASH conditions and practices among participating households were chosen from Ram’s 2013 Practical Guidance for Measuring Handwashing Behavior in Water and Sanitation Programs (38), UNICEF’s 2013 Handwashing Promotion Monitoring and Evaluation Module (39), WHO’s 2006 Core Questions on Drinking-water and Sanitation for Household Surveys (40), as well as the 2011 Demographic and Health Survey (DHS) (41). The caregiver’s hands and the child’s hands were visually inspected for cleanliness. A number of studies have used visual inspection of respondents' hands to characterize their degree of cleanliness. Pickering et al. (42) found that visible dirt on palms, finger pads, or under nails is associated with increased microbiological contamination of hands. Another study in Bangladesh found that a child having visibly clean finger pads was associated with reduced diarrhea prevalence (43). Our study used the same methodology for inspecting hands, which included a three-point scale denoting "clean," "no visible dirt but unclean appearance," and "visible dirt" regarding the palms, finger pads, and finger nails (38). During data collection training, data collectors underwent examples of proper scoring, with several tests of inter-rater reliability (i.e. where different enumerators coded the same level of cleanliness for a pair of hands).

Use of improved water source and sanitation facilities was based on the WHO definitions (40, 41). Respondents were asked if they take action to treat water, following DHS format (41). Water storage containers were assessed for having fitted lids (44). The Centers for Disease Control and Prevention suggests that drinking water storage containers should have fitted lids to avoid contamination (45). Hygiene was assessed by direct observation of a hand washing demonstration (38, 39), knowledge regarding five critical times for hand washing (39, 41, 44), and the frequency in which the child is bathed. Although the frequency of bathing a child is not as commonly as other indicators used in WASH assessments, it is a proxy indicator for hygiene practices in childcare. A recent study in Nepal by Khatri et al. (46) found that children were less likely to be underweight if they were bathed on a daily basis. **Table 3** contains information on the definition and scoring of each indicator relating to WASH.

Table 3.
WASH indicators from the HH survey[1]

Indicator	Definition and scoring	Range
Cleanliness of caregiver's hands	Observed cleanliness of caregiver's hands. Respondents received a score of 1 if the caregiver's hands were observed to be clean and 0 if the hands were observed to be unclean (38, 42).	0,1
Cleanliness of child's hands	Observed cleanliness of child's hands. Respondents received a score of 1 if the child's hands were observed to be clean and 0 if the hands were observed to be unclean (38, 42).	0,1
Improved water source	If drinking water comes from improved water sources. Respondents received a score of 1 if all water sources were improved sources of drinking water, and 0 if any water sources were unimproved. Improved water sources included: piped water into dwelling, piped water into yard/plot, public tap or standpipe, tube well or borehole, protected dug well, protected spring, and rainwater. Unimproved water sources included: unprotected spring, unprotected dug well, cart with small tank/drum, tanker-truck, or surface water (40).	0,1
Lids on water storage containers	If water storage containers have lids. Respondents received a score of 1 if all water storage containers were observed to have lids and 0 if any did not have lids (45).	0,1
Treat drinking water	If action is taken to treat or make the drinking water safe. Respondents were assigned a score of 1 if action was taken to make the drinking water safe for human consumption and 0 if no action was taken. Actions for making drinking water safe included: boiling, bleaching, adding chlorine, straining through a cloth, use of water filer, solar disinfection, and let it stand and settle (41).	0,1
Hand washing	Used soap or ash during a hand washing demonstration. Respondents were observed during a hand washing demonstration. If soap or ash was used during the demonstration, respondents were assigned a score of 1 and 0 if neither soap nor ash were used (38, 41).	0,1
Knowledge of critical times for caregiver hand washing	Knowledge of critical times for hand washing. The five critical times for washing hands include: 1) after defecation, 2) after cleaning a child, 3) before preparing food, 4) before feeding a child, and 5) before eating, as defined by UNICEF (41, 44). Respondents were assigned a 1 for listing all critical times points and 0 for not listing all critical time points for washing hands.	0,1

Frequency of bathing child	Number of times the enrolled child was bathed in the previous week. Respondents were assigned 0 if the child was bathed less than once per day and 1 if the child was bathed at least once per day during the previous week (46).	0,1
Improved sanitation facility	If HH uses an improved sanitation facility. Respondents received a score of 1 if HH members used an improved sanitation facility, and 0 if HH members used an unimproved sanitation facility. Improved sanitation facilities included: flush toilet, piped sewer system, septic tank, flush/pour flush to pit latrine, ventilated improved pit latrine, or pit latrine with slab. Unimproved sanitation facilities included: pit latrine without slab, bucket, hanging toilet or hanging latrine, or no facilities/bush/field (40).	0,1

[1] HH, household; WASH, water, sanitation, and hygiene.

Statistical Analysis

Initially, we planned to construct an SES index using principal component analysis (PCA) (47), a technique that creates a single variable (the index) through the summation of individual weighted variables. We conducted PCA on various combinations of indicators relating to maternal education, household characteristics, asset ownership and livestock ownership. However, individual indicators were not correlated enough, as indicated by Cronbach's alphas below 0.65, to generate one overall SES index. We estimate the low correlation between indicators may be due to the population being extremely homogeneous, as many of the indicators lacked variability. For example, 97% of caregivers' highest level of education is primary school only (less than a 8 years of schooling). As shown by Psaki et al. (29), education level often correlates with wealth. However, in this study, there is no correlation between number of HH assets owned and education completed by caregivers, with the exception of the very few (<3%) who completed education beyond primary school. Therefore, rather than using one overall SES index, the following individual variables were included in the final regression model: maternal education, number of rooms in a house, ownership of any livestock, and number of household assets (out of 11 total) (**Table 1**).

Bivariate analysis was conducted using student's t test for continuous variables and chi-squared for binary variables with adjustment for clustering at the health clinic level in order to compare individual indicators between HHs with children who sustained recovery for 12 month following discharge from SFP and those that did not. P-values < 0.05 were considered to be statistically significant. All statistical analysis was conducted using Stata Version 13.0 (StataCorp LP, College Station, TX).

Binary logistic regression was used to identify which indicators were associated with sustained recovery while accounting for other factors. Cluster-adjusted robust standard errors were used to account for the clustering at the health clinic level. Variables used in the full model included sex, age at the time of admission to SFP, whether the child had fever during the 2 weeks prior to admission into the SFP, whether the child had diarrhea during the 2 weeks prior to admission into the SFP, discharge MUAC, discharge WHZ score, years of education completed by the caregiver, number of rooms in the house, whether any livestock was owned, number of HH assets owned (out of 11), whether the child was currently breastfeeding at the time of SFP discharge (for children under 24 months) or whether the child continued to breastfeed up to age 24 months (for children over 24 months), minimum dietary diversity, minimum meal frequency, average HFAIS score from all follow-up visits, if all drinking water was retrieved from improved water source, use of an improved sanitation facility, cleanliness of caregiver's hands, cleanliness of child's hands, and whether the child was bathed daily during the previous week.

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Chapter 1. Including whey protein and permeate in ready-to-use supplementary food improves recovery rates in children with moderate acute malnutrition[3]

Abstract

Background: The utility of dairy ingredients in supplementary foods used in the treatment of childhood moderate acute malnutrition (MAM) remains unsettled.

Objective: We evaluated the effectiveness of a peanut-based ready-to-use supplementary food (RUSF) with soy protein compared with a novel RUSF containing dairy ingredients in the form of whey permeate and whey protein concentrate in the treatment of children with MAM.

Design: We conducted a randomized, double-blinded clinical effectiveness trial involving rural Malawian and Mozambican children 6-59 months old with MAM treated with either soy RUSF or a novel whey RUSF treatment for up to 12 weeks.

Results: The proportion of children that recovered from MAM was significantly higher in the group that received whey RUSF (84%), compared to soy RUSF (81%) ($P < 0.04$; risk difference 3.4%, 95% CI: 0.3%, 6.6%). Children who consumed whey RUSF also demonstrated better growth parameters, with a higher mean mid-upper arm circumference (MUAC) at the time of discharge ($P < 0.009$), greater MUAC gain during the course of treatment ($P < 0.003$), higher mean weight-for-height Z-score at discharge ($P < 0.008$), and greater weight gain ($P < 0.05$). No significant differences were identified in length gain or time to recovery between the two groups.

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Conclusion: This study highlights the importance of milk protein in the treatment of MAM, as the use of a novel whey RUSF resulted in modestly higher recovery rates and improved growth than soy RUSF, even though the whey RUSF supplement provided less total protein and energy than the soy RUSF.

Introduction

Several supplementary food products, notably peanut paste-based ready-to-use supplementary foods (RUSF), have been developed and successfully used for the treatment of moderate acute malnutrition (MAM) in children (1-5). Nevertheless, the optimal quality, quantity, and source of protein used in these foods to optimize nutritional outcomes and survival is still debated (6). While dairy protein is known to be important for growth (7), evidence regarding its necessity specifically in the treatment of MAM is lacking.

Studies suggest that dairy protein – as opposed to plant-based protein – increases lean body mass, accelerates linear growth, and improves recovery outcomes in undernourished populations (8-10). The biological explanation for these improved outcomes may be related to bioactive peptides, growth stimulating factors, a high concentration of branched chain amino acids, and/or lactose (11-14). At its most basic level, milk protein consists of two major components: whey and casein. While casein stimulates production of insulin-like growth factor-1 (15), whey has been linked to muscle restoration, bone growth, immune function, and intestinal integrity (11, 12, 14, 16-19).

Despite the popularity of whey, evidence supporting its use in supplementary foods for malnourished children is limited (6). In this double-blinded, randomized controlled clinical effectiveness trial, we compare two RUSF products (a soy RUSF versus a novel whey RUSF) in the treatment of children with MAM.

Methods

Subjects and Setting

Children aged 6-59 months with MAM, as defined by a mid-upper-arm circumference (MUAC) of 11.5-12.4 cm without bipedal edema (20, 21), were recruited at 18 rural sites in southern Malawi from February 2013 to November 2014, including some sites in border areas serving children from Mozambique. We chose to use MUAC as the anthropometric criterion for entry and exit in this study, in contrast to weight-for-height Z-score (WHZ) used in our previous studies on MAM (1-3, 5, 22, 23), given the compelling evidence that MUAC is better suited for identifying those malnourished children at highest risk for mortality (24-27).

Children in this area almost universally come from subsistence farming families where their staple crop, maize, is harvested following a single annual rainy season (28). Animal-source foods are rarely consumed and are estimated to contribute only 2-7% of the energy intake of infants (excluding breast milk) in this population (2, 29). Prevalence of acute malnutrition typically peaks each year from December to March, just prior to the harvest in April. More than 40% of Malawian children under 5 years old are stunted, and the under-5 mortality rate is 6.8% (30).

Acceptability Testing

Prior to the randomized controlled clinical trial, acceptability testing of the novel whey RUSF formula was conducted following a protocol modeled on that of Phuka et al. (31). The purpose was to determine the taste acceptability and physical tolerance of the new RUSF formula. Children 6-59 months without severe acute malnutrition (SAM) were identified at one of the nutrition clinics used for the main clinical trial and randomly assigned to one of the two RUSF interventions at doses ranging from 6 teaspoons (30 mL) for a 5 kg child to 15 teaspoons (74 mL) for a child over 10 kg. Feeding was directly observed at the site. The time it took for the child to consume the entire serving of food was measured, as well as the amount of food remaining if not completely consumed. Caregivers were asked to estimate the supplement's palatability and overall likability on a 5-point hedonic scale that graphically illustrated a series of human faces with varying degrees of smile or discontent. Caretakers were then provided the food to continue daily feeding at home and returned on the fourth day to report again on the child's tolerance of the food and any adverse reactions, including diarrhea.

Study Design

The trial itself was a randomized, double-blinded, controlled clinical effectiveness trial in which participants were randomized to receive one of two supplementary foods and assessed for recovery from MAM. The primary outcome was recovery from MAM, defined as achieving a MUAC of 12.5 cm or greater without bipedal edema within 12 weeks of therapy. If children did not recover, they were categorized as having continued MAM, developing SAM (MUAC < 11.5 cm and/or bipedal edema), dying, or defaulting (failing to return for three consecutive visits). Secondary outcomes consisted of changes in MUAC, weight, and length; time to recovery; and any adverse events.

A minimum sample size of 1073 children in each group was sought to detect an improved recovery rate in the novel whey RUSF group of 88%, compared to an expected recovery rate of 84% in the soy RUSF group (1-3), assuming 95% sensitivity, 80% power, and an incomplete follow-up rate of 10% (32).

Random allocation was performed by caregivers drawing opaque envelopes that contained one of two coded papers corresponding to either whey RUSF or soy RUSF. This code was accessible only to the food distribution personnel, who do not assess participant outcomes, determine eligibility, or analyze data. The two RUSF formulations had similar color, taste, smell, and packaging. If there were two study participants from the same household, both children received the same type of food to reduce the likelihood of confusing the assigned interventions.

Study Foods

Whey is the serum or liquid part of milk that is a byproduct of cheese and curd manufacturing. Whey proteins are fractionated from the whey and dried to make whey protein concentrate (WPC) and other ingredients (12). The most common formulation of WPC, known as WPC80, typically contains 80% protein, 10% lactose, and minerals (33). In the whey fractionation process, after the extraction of whey proteins, whey permeate remains. Whey permeate is high in lactose (minimum 85%) and generally marketed as a sweet bulking and browning ingredient, flavor enhancer, and mild milk flavor provider. In the context of treating children for MAM, the major postulated potential benefit of whey permeate is its high lactose content. Lactose is a disaccharide found naturally in milk and serves as a primary energy source for breastfed infants. With ample lactase enzymes in the small intestine, lactose hydrolyzes into monosaccharides used as energy. In infants, lactose provides energy needed for rapid growth, has a lower glycemic index and cariogenic effects than sucrose (33), and may improve the absorption of growth-supporting minerals such as calcium (14).

To balance the conflicting demands of providing sufficient quantities of protein to meet the minimum World Health Organization (WHO) protein recommendations for supplementary foods (34) while developing a novel RUSF that is affordable for widespread usage, a combination of 4.9% WPC80 and 18.7% whey permeate (Arla Foods Ingredients Group P/S, Aarhus, Denmark) was used in the whey RUSF. Peanut paste, sugar, palm oil, soy oil, emulsifier, and a customized micronutrient premix constituted the balance of the whey RUSF. The soy RUSF recipe used has previously been shown effective in treating children with MAM (1, 2) and served as the control RUSF. This soy RUSF included extruded soy flour, peanut paste, sugar, palm oil, soy oil, a micronutrient premix, and dicalcium phosphate or calcium carbonate (Roche, Mumbai, India). The soy RUSF contained no animal-source proteins (**Table 1**).

In order to maintain blinding, the volume and weight of RUSF provided (on a per-kilogram basis) was the same between the two interventions, although this led to some differences in nutrient composition (**Table 2** and **Supplemental Tables 1 and 2**). Most notably, the total amount of protein provided by soy RUSF was about 50% more than whey RUSF. The Protein Digestibility-Corrected Amino Acid Score (PDCAAS) was higher in whey RUSF, and the Digestible-Indispensable Amino Acid Score (DIAAS) was similar in both foods (35, 36).

Both foods were produced by Project Peanut Butter in Blantyre, Malawi (37) and underwent quality assurance and safety testing for aflatoxin and microbial contamination at the Malawi Bureau of Standards and at Eurofins Scientific Inc., Des Moines, Iowa, USA. The production cost of soy RUSF was $2.78/kg and was $3.13/kg for whey RUSF.

Subject Participation

Children were evaluated for acute malnutrition by nutrition research assistants and senior pediatric research nurses, trained and supervised by the senior investigators. MUAC was measured with a standard insertion tape to the nearest 0.1 cm (TALC, Harpenden, UK). Weight was measured using an electronic scale to the nearest 5 g (Seca 334, Hamburg, Germany). Length was measured to the nearest 0.1 cm using a rigid length board (Seca 417, Hamburg, Germany). Children were also evaluated for kwashiorkor by assessing for bilateral pitting edema. The caregivers of children who met enrollment criteria were asked to give verbal and written consent for participation in the study prior to randomization. Children with chronic illnesses (not including HIV or TB), a known allergy to milk, soy, or peanuts, those who had received treatment for acute malnutrition in the previous three months, and those who were not permanent residents of the vicinity near the clinic site were excluded.

Once enrolled, each child's caregiver was interviewed regarding the child's demographic characteristics, appetite, infectious symptoms, and known food allergies. Each caregiver also completed the Household Food Insecurity Access Scale (HFIAS) (38) and a dairy-focused food frequency questionnaire.

A two-week supply of either soy RUSF or whey RUSF at a dose of approximately 75 kcal/kg/d was provided along with nutrition counseling and instructions for proper feeding of the RUSF. The number of food packets distributed to each child varied according to weight. Caretakers were instructed to feed the RUSF only to the enrolled child, to provide additional complementary foods and continue breastfeeding (if applicable), and to ration the allotted food to last until the next fortnightly distribution. If the child was a twin, twice the amount of food was given to the caregiver to feed both children in order to limit sharing between the twins and increase the likelihood that the enrolled child received the full ration intended.

Children were scheduled for follow-up appointments on a fortnightly basis. At each subsequent visit, anthropometric measurements were repeated and caretakers reported on the child's clinical symptoms. If the child remained moderately acutely malnourished, an additional two-week ration of RUSF was provided. Children that became severely malnourished during the course of the treatment were treated as outpatients with ready-to-use therapeutic food (RUTF) (39) or, if necessary, at an inpatient nutritional rehabilitation center. Children that missed appointments were sought by the research team in their homes and assessed there if needed.

Ethical Approval

The study was approved by the University of Malawi's College of Medicine Research and Ethics Committee, Washington University's Human Research Protection Office, and Tufts University's Internal Review Board. Permission to conduct the study was obtained by each site's District Health Officer and/or District Nutritionist.

Statistical Analyses

All data were double-entered into an Access (Microsoft Corp., Redmond WA) database and compared to original paper charts to resolve any discrepancies. Anthropometric indices were based on the World Health Organization's 2006 Child Growth Standards (40), calculated using the WHO Anthro software (WHO, Geneva).

Rates of MUAC and length gain were calculated in mm/d over the duration of each participant's time in the study. Weight gain was calculated in g/kg/day for the duration of the study as well as from enrollment to the second follow-up visit (or first visit for those for whom only one visit was recorded). Intention-to-treat analyses were used, and all tests were two-sided. Dichotomous outcomes were compared with either Fisher's exact test or the chi-squared test; the Student t-test was used for comparing continuous variables. P-values less than 0.05 were considered to be statistically significant. Statistical analyses were performed in Stata Version 13.0 (StataCorp LP, College Station, TX).

Results

Acceptability Testing

A total of 60 children aged 6-51 months were enrolled in the acceptability trial; all but one returned for the follow-up questionnaire. The average times for children to consume the two RUSF foods were similar at the initial visit (**Supplemental Table 3**). Both foods were deemed to be highly acceptable based on the hedonic scale ratings and comments from the caregivers. One child in the soy RUSF group and 2 children in the whey RUSF group had a new onset of diarrhea after starting RUSF, all lasting 1-2 days.

Randomized Controlled Trial

A total of 2259 children were originally enrolled in the study; 29 were excluded due to enrollment errors, leaving 1086 for final analysis in the soy RUSF group and 1144 in the whey RUSF group (**Figure 1**). Demographic, anthropometric, clinical, social, and dietary intake characteristics were similar in the two groups, with the exception of a slightly higher rate of HIV-positive mothers in the soy RUSF group (**Table 3** and **Supplemental Table 4**).

The percentage of children with MAM that successfully recovered, defined as MUAC ≥ 12.5 cm without peripheral edema within 12 weeks of treatment, was higher in the whey RUSF group at 83.9% compared to the soy RUSF group at 80.5% ($P < 0.04$; RR= 1.043, 95% CI: 1.003, 1.084) (**Table 4** and **Figure 2**). The risk difference for recovery for the whey RUSF group compared to soy RUSF was 3.4% (95% CI: 0.3%, 6.6%). The proportion of children who developed SAM during the course of treatment was similar in both groups: 11.8% in the soy RUSF group and 10.2% in the whey RUSF group ($P = 0.27$). The proportion of children who remained moderately malnourished despite 12 weeks of treatment and the number who defaulted were also similar between the two groups.

Children of mothers known to be HIV-positive recovered 78.3% of the time, compared to 82.8% among children of mothers known to be HIV-negative ($P = 0.11$). In the whey RUSF group, 80.4% of children with HIV-positive mothers recovered, compared to 76.5% in the soy RUSF group ($P = 0.51$). Logistic regression modeling using backward elimination did not show maternal HIV status to be a significant factor in recovery, but the type of RUSF administered continued to be a significant factor in recovery ($P < 0.03$).

Although the average MUAC at enrollment was similar between the two groups, the average MUAC at final measurement in the whey RUSF group was greater than in the soy RUSF group ($P < 0.009$). Given that the time to recovery was similar between the two groups, the average daily MUAC gain was also thus greater in the whey RUSF group ($P < 0.003$). The whey RUSF group also demonstrated a greater rate of weight gain over the first 2-4 weeks of therapy ($P < 0.05$), higher WHZ at final measurement ($P < 0.008$), and greater improvements in WHZ than the soy RUSF group ($P < 0.02$).

Given the relatively short follow-up period of the study, no significant difference in the average length gain between the two groups was identified. No significant adverse events that could be attributed to the intervention foods were identified in either treatment group.

Discussion

In this randomized, double-blinded controlled clinical trial, we demonstrate that removing extruded soy flour and including whey permeate and WPC80 in a proven RUSF recipe improves nutritional recovery and anthropometry when treating children in Malawi with MAM. The patients enrolled in this study were younger and had higher WHZ scores at enrollment than those enrolled in previous studies on children with MAM conducted in the same area (1-3, 5, 22, 23). The use of MUAC in the current study, as opposed to WHZ in previous studies, may explain the relatively lower recovery rates and higher rates of progression to SAM than have been observed previously. Nevertheless, given the increasing operationalization of MUAC as the entry and exit criterion for supplementary and therapeutic feeding programs, including its potential use as a screening tool by caretakers themselves at home (41), this current study arguably provides a more contemporary insight on outcomes that may be expected for children with MAM.

This study provides the first specific evidence to support the value of whey ingredients in RUSF to treat MAM. While prior studies have shown positive correlations between the consumption of dairy protein and improved outcomes in undernourished populations (8-10), it was unclear whether those findings were due specifically to the type of protein in the food or simply the total amount of protein (6). In this study, despite providing 33% less total protein and nearly 8% less total energy, outcomes were better in children receiving whey RUSF than those receiving soy RUSF.

This result is consistent with previous studies demonstrating the superior performance of dairy protein in the treatment of acute malnutrition. When treating children for SAM, substituting soy for dry skim milk in RUTF resulted in lower recovery rates and poorer growth outcomes in a similar population of Malawian children (10). However, substituting WPC for dry skim milk in a novel RUTF recipe produced recovery rates similar to the standard dry skim milk formulation (42). For children with MAM, a soy/whey RUSF led to a similar recovery rate as soy RUSF (2); yet those treated with the soy/whey RUSF were more likely to remain well-nourished during a 12-month follow-up period (22, 23).

Whey is known for its high quality amino acid (AA) profile when compared to plant-sourced proteins (**Supplemental Table 5**). Whey protein is an excellent source for branched-chain amino acids (15), which are metabolized by muscle and counteract lean tissue breakdown (42) – a critical step in the recovery from acute malnutrition. Whey supplementation has also been shown to increase fasting insulin and facilitate the retention of absorbed AAs (12, 15, 17).

Other factors may explain the improved outcomes observed in the whey RUSF group, including the presence of bioactive peptides such as α-lactalbumin, β-lactoglobulin, serum proteins, lactoferrin, and immunoglobulins (12, 33). These compounds have important biological functions related to growth and immune system support, such as iron binding, tissue repair, and resistance to infections (12, 14). Any of these substances which support the immune system may contribute to whey RUSF's superior recovery rate, considering malnourished children's increased susceptibility to infections (43).

The prebiotic effects of lactose found in whey permeate may also contribute to recovery. Feeding large amounts of lactose has shown to stimulate bifidobacteria and lactobacilli and increase short-chain fatty acids (SCFAs) in weaning piglets (18, 19). Increased lactose consumption has also been shown to increase intestinal weight and body weight in turkeys (44). It is possible that lactase activity is reduced in malnourished children due to their compromised intestinal barriers (45) and that this secondary lactose deficiency causes undigested lactose to be fermented into SCFAs, which improve colonic microbiome composition (17).

Although our study may indirectly support a prebiotic effect of lactose, others have had mixed results with prebiotics. A randomized trial in Malawi examining the addition of a different type of prebiotic (lactic acid bacteria) to RUTF did not improve recovery rates from SAM (46). A study in Bangladesh demonstrated the microbial composition of the gut in malnourished children only improved for one month after initial recovery with therapeutic food containing milk (and thus some lactose) (47).

Another factor in recovery may be the higher content of the anti-nutrient phytic acid in soy RUSF (more than double that found in whey RUSF), which inhibits protein digestibility and mineral absorption (14).

Whey RUSF performed better than soy RUSF, even with lower total energy and protein content, highlighting the benefits of dairy-based food. Many nutrition and public health experts have recommended the increased use of dairy products to improve the quality of supplemental foods used in the treatment of MAM (48). However, the use of animal-sourced protein is generally more expensive than plant-based protein. For a typical child weighing 7 kg, the total amount of RUSF provided until recovery is just over 3 kg, with whey RUSF costing approximately $1.36 more than soy RUSF per child recovered. In the larger context of the operational costs of a supplementary feeding program that includes staff, anthropometric equipment, logistical support, and facilities, this additional cost is quite minimal for the significantly higher recovery rate achieved.[4] While some have questioned whether the benefits of including dairy protein are worth the additional expense (6), this study provides evidence that their inclusion leads to improved outcomes in children with MAM with only a marginal increase in cost.

[4] Exact costs are presented in Addendum 1 to Chapter 1

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Tables and Figures

Table 1. Ingredient composition of the two study foods, as a percentage of total weight[1]

Ingredient	Soy RUSF	Whey RUSF
Peanut paste	26.9	29.4
Sugar	25.7	24.4
Extruded soy flour	24.0	-
Whey permeate	-	18.7
Whey protein concentrate (WPC80)	-	4.9
Palm oil	10.0	10.0
Soy oil	7.3	7.6
Micronutrient mixture	4.6	3.5
Emulsifier	1.5	1.5

[1] RUSF, ready-to-use supplementary food.

Table 2. Nutrient composition of intervention foods, based on a typical daily ration for a child with MAM weighing 7 kg[1]

	Soy RUSF	**Whey RUSF**
Total weight (g)	105.35	105.35
Energy (kcal)	559.52	516.34
Total lipids (g)	36.84	35.74
Total protein (g)	17.06	11.42
Protein Digestibility-Corrected Amino Acid Score (PDCAAS)	0.78	1.00
Digestible Indispensable Amino Acid Score (DIAAS)	0.74	0.72
Minerals		
Biotin (µg)	13.01	10.54
Calcium (mg)	659.71	519.13
Copper (mg)	0.96	0.55
Iodide (µg)	97.86	85.46
Iron (mg)	9.42	9.44
Magnesium (mg)	247.20	149.87
Manganese (mg)	2.00	1.17
Phosphorus (mg)	793.53	600.33
Potassium (mg)	1195.91	762.84
Selenium (µg)	25.00	18.54
Sodium (mg)	3.52	31.95
Zinc (mg)	14.36	10.58
Vitamins		
Folic acid (µg)	98.50	255.61
Niacin (mg)	16.18	13.14
Pantothenic acid (mg)	3.63	2.64
Riboflavin (mg)	2.74	2.25
Thiamin (mg)	0.55	0.53
Vitamin A (RAE) (µg)	1288.92	1051.26
Vitamin B-6 (mg)	1.40	1.08
Vitamin B-12 (µg)	3.25	2.63
Vitamin C (mg)	97.58	79.01
Vitamin D (µg)	13.01	10.54
Vitamin E (µg)	20.99	16.55
Vitamin K (µg)	31.97	14.60
Anti-Nutrient		
Phytic acid (g)	0.45	0.21

[1] MAM, moderate acute malnutrition; RUSF, ready-to-use supplementary food.

Table 3. Enrollment characteristics of children treated for moderate acute malnutrition[1]

	Soy RUSF (n = 1086)	**Whey RUSF** (n = 1144)
Female	639 (58.9)	688 (60.2)
Age (mo)	16.5 ± 8.9[2]	16.4 ± 9.3
6-11 mo	415 (38.8)	461 (40.9)
12-23 mo	471 (44.0)	450 (39.9)
24-59 mo	184 (17.2)	217 (19.2)
MUAC (49)	12.1 ± 0.27	12.1 ± 0.27
Weight (kg)	7.14 ± 1.20	7.14 ± 1.29
Length (49)	70.7 ± 6.90	70.8 ± 7.52
WHZ	-1.88 ± 0.71	-1.85 ± 0.73
HAZ	-2.88 ± 1.36	-2.84 ± 1.36
WAZ	-2.95 ± 0.80	-2.93 ± 0.79
Primary caretaker is mother	1022/1060 (96.4)	1073/1114 (96.3)
Father is alive	1031/1058 (97.4)	1093/1121 (97.5)
Child breastfed	776/1053 (73.7)	800/1117 (71.6)
Mother is known to be HIV+ *	119/908 (13.1)	94/958 (9.8)
Child eating well	992/1057 (93.9)	1057/1110 (95.2)
HFIAS Score	7.4 ± 6.4	7.3 ± 6.0
Food Secure	205 (19.7)	199 (18.0)
Mild Food Insecurity	54 (5.2)	63 (5.7)
Moderate Food Insecurity	193 (18.5)	213 (19.2)
Severe Food Insecurity	591 (56.7)	633 (57.1)
Fever in 2 wk prior to enrollment	704/1082 (65.1)	736/1143 (64.4)
Diarrhea in 2 wk prior to enrollment	644/1082 (59.5)	677/1143 (59.2)

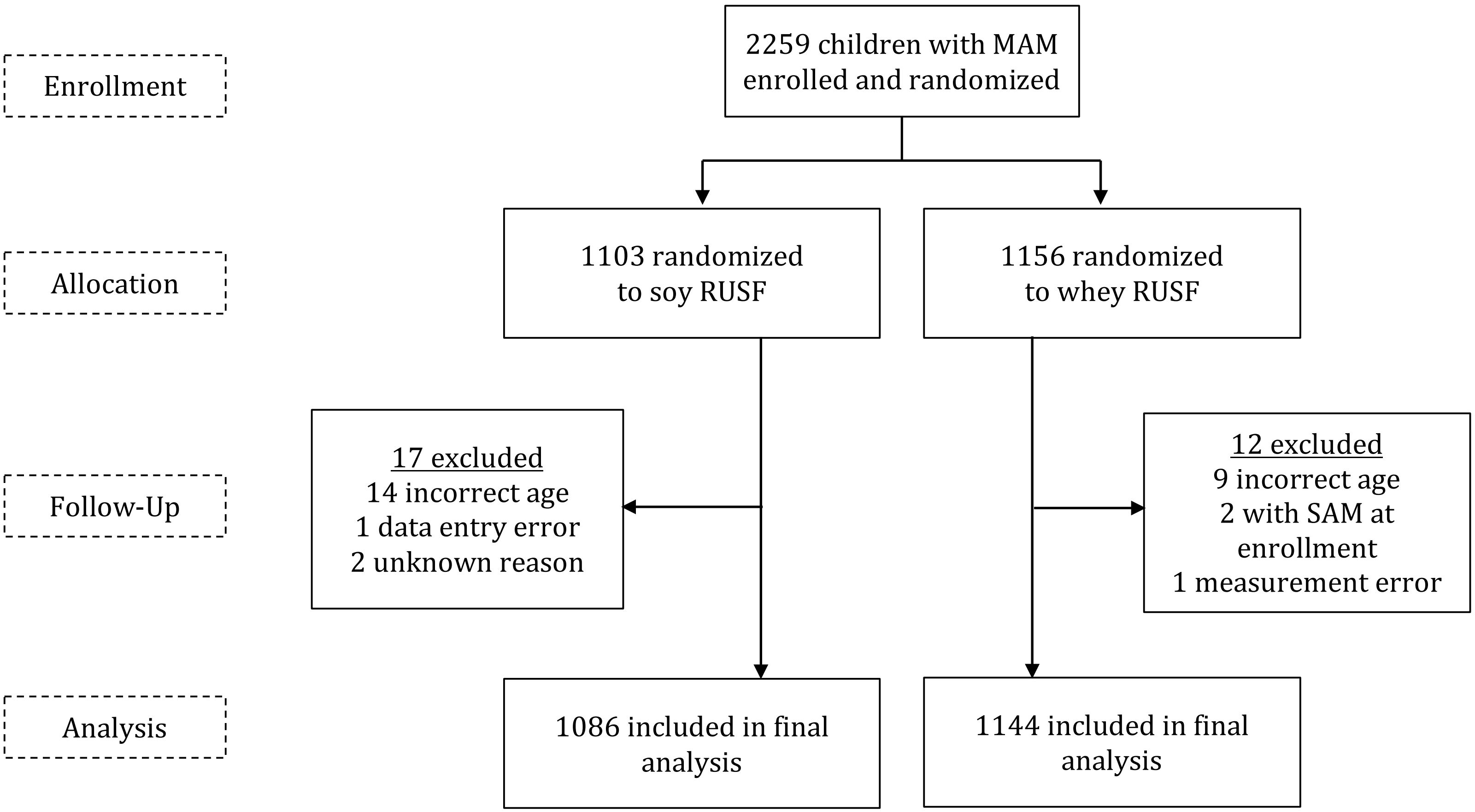
[1] Values are means ± SDs, n (%) or n/n (5). HAZ, height-for-age Z-score; HFIAS, Household Food Insecurity Access Scale (0-27); MUAC, mid-upper-arm circumference; RUSF, ready-to-use supplementary food; WAZ, weight-for-age Z-score; WHZ, weight-for-height Z-score. * $P < 0.03$ by Fisher's exact test.

Table 4. Outcomes of children treated for MAM with either Soy RUSF or Whey RUSF[1]

	Soy RUSF (n = 1086)	**Whey RUSF** (n = 1144)	***P* value**
Recovered	874 (80.5)	960 (83.9)	0.039
Time to recovery (d)	30.4 ± 20.1[3]	29.3 ± 19.0	0.22
Did not recover	212 (19.5)	184 (16.1)	0.039
Developed SAM	128 (11.7)	117 (10.2)	0.27
Remained moderately malnourished	52 (4.8)	49 (4.3)	0.64
Default	28 (2.6)	16 (1.4)	0.064
Died	4 (0.37)	2 (0.17)	0.44
MUAC at final visit	12.59 ± 0.56	12.66 ± 0.53	0.0088
MUAC gain (mm/d)	0.22 ± 0.28	0.26 ± 0.27	0.0025
WHZ at final visit	-1.18 ± 0.90	-1.08 ± 0.86	0.0077
WHZ change to final visit	0.70 ± 0.66	0.77 ± 0.62	0.012
Weight gain to final visit (g/kg/d)	2.79 ± 2.16	2.95 ± 2.04	0.11
Weight gain to 2nd follow-up visit[2] (g/kg/d)	2.65 ± 2.30	2.88 ± 2.18	0.042
Length gain to final visit (mm/d)	0.29 ± 0.29	0.30 ± 0.28	0.18

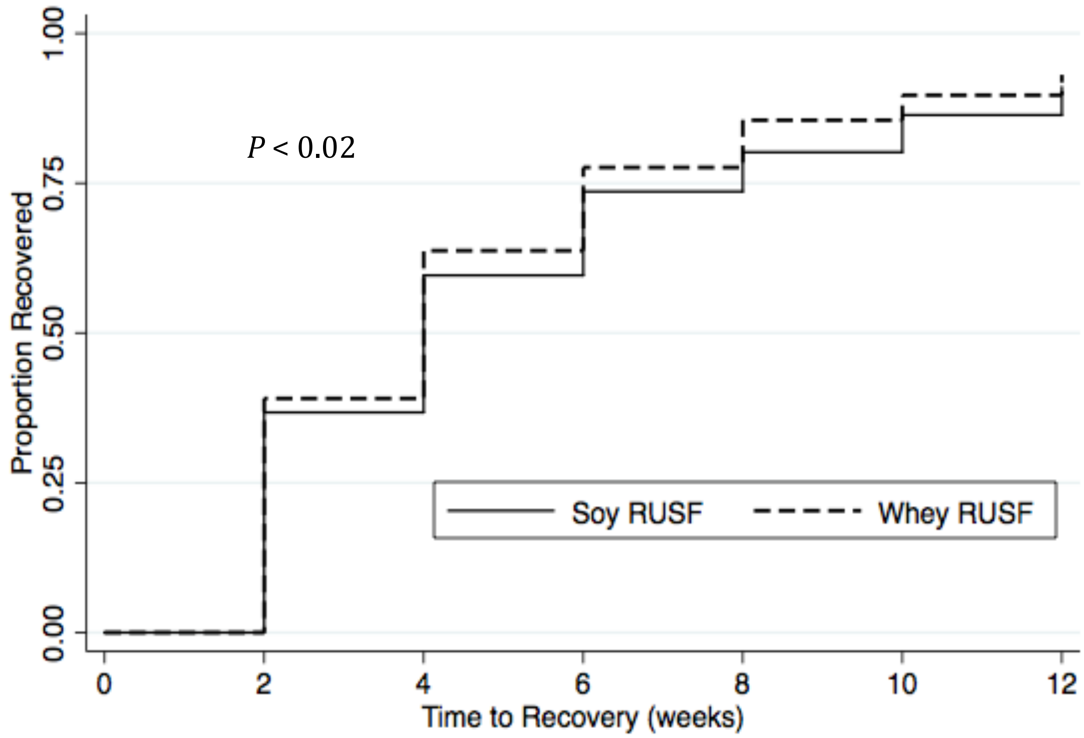
[1] Values are mean ± SDs. HAZ, height-for-age Z-score; MAM, moderate acute malnutrition; MUAC, mid-upper-arm circumference; RUSF, ready-to-use supplementary food; SAM, severe acute malnutrition; WHZ, weight-for-height Z-score.
[2] Or 1st follow-up visit for those with only 1 follow-up.

Figure 1. Flow of participants through the randomized controlled clinical trial[1]



[1] MAM, moderate acute malnutrition; RUSF, ready-to-use supplementary food; SAM, severe acute malnutrition.

Figure 2. Kaplan-Meier curves for time to recovery[1] in children with MAM receiving either Soy RUSF or Whey RUSF[2]



No. at Risk						
Soy RUSF: 1086	687	466	341	288	243	212
Whey RUSF: 1144	697	442	311	243	209	184

[1] Defined as achieving a mid-upper-arm circumference of at least 12.5 cm without edema.
[2] MAM, moderate acute malnutrition; RUSF, ready-to-use supplementary food

Supplemental Table 1. Nutrient composition of soy RUSF, based on a typical daily ration (105.35 g) for a child with MAM weighing 7 kg[1]

	Soy Flour	Custom Micronutrient Mix	Sugar, Palm Oil, Soy Oil, Peanut Paste, Emulsifier	Total
Total weight (g)	25.28	4.79	75.28	105.35
Energy (kcal)	115.52		444.00	559.52
Total lipids (g)	5.04		31.80	36.84
Total protein (g)	10.35		6.71	17.06
Protein Digestibility-Corrected Amino Acid Score (PDCAAS)				0.78
Digestible Indispensable Amino Acid Score (DIAAS)				0.74
Minerals				
Biotin (µg)		13.01		13.01
Calcium (mg)	6.57	637.55	15.58	659.71
Copper (mg)	0.28	0.49	0.19	0.96
Iodide (µg)		97.58	0.27	97.86
Iron (mg)	3.11	5.66	0.65	9.42
Magnesium (mg)	60.68	136.62	49.90	247.20
Manganese (mg)	0.76	0.65	0.59	2.00
Phosphorus (mg)	139.06	552.98	101.49	793.53
Potassium (mg)	429.83	579.00	187.08	1195.91
Selenium (µg)	1.90	20.82	2.29	25.00
Sodium (mg)	1.82		1.70	3.52
Zinc (mg)	1.06	12.36	0.94	14.36
Vitamins				
Folic acid (µg)	57.39		41.11	98.50
Niacin (mg)	0.83	11.51	3.83	16.18
Pantothenic acid (mg)	0.31	2.93	0.40	3.63
Riboflavin (mg)	0.24	2.47	0.03	2.74
Thiamin (mg)	0.10	0.33	0.12	0.55
Vitamin A (RAE) (µg)	9.25	1279.66		1288.92
Vitamin B-6 (mg)	0.09	1.24	0.07	1.40
Vitamin B-12 (µg)		3.25		3.25
Vitamin C (mg)		97.58		97.58
Vitamin D (µg)		13.01		13.01
Vitamin E (µg)	0.50	16.26	4.23	20.99
Vitamin K (µg)	17.95		14.02	31.97
Anti-Nutrient				
Phytic acid (g)				0.45

[1] MAM, moderate acute malnutrition; RUSF, ready-to-use supplementary food.

Supplemental Table 2. Nutrient composition of whey RUSF, based on a typical daily ration (105.35 g) for a child with MAM weighing 7 kg[1]

	WPC80	Whey Permeate	Custom Micro-nutrient Mix	Sugar, Palm Oil, Soy Oil, Peanut Paste, Emulsifier	Total
Total weight (g)	5.16	19.70	3.69	76.80	105.35
Energy (kcal)	20.18	19.00		477.16	516.34
Total lipids (g)	0.22	0.02		35.50	35.74
Total protein (g)	3.98	0.10		7.33	11.42
Protein Digestibility-Corrected Amino Acid Score (PDCAAS)					1.00
Digestible Indispensable Amino Acid Score (DIAAS)					0.72
Minerals					
Biotin (µg)			10.54		10.54
Calcium (mg)	20.60	20.65	460.91	16.98	519.13
Copper (mg)			0.34	0.21	0.55
Iodide (µg)		6.19	79.01	0.26	85.46
Iron (mg)	0.04		8.69	0.71	9.44
Magnesium (mg)	3.28	5.16	86.91	54.51	149.87
Manganese (mg)			0.53	0.65	1.17
Phosphorus (mg)	15.90	25.81	447.74	110.88	600.33
Potassium (mg)	27.77	61.95	468.81	204.32	762.84
Selenium (µg)			16.07	2.48	18.54
Sodium (mg)	9.45	20.65		1.86	31.95
Zinc (mg)	0.02		9.53	1.03	10.58
Vitamins					
Folic acid (µg)			210.70	44.91	255.61
Niacin (mg)			8.95	4.19	13.14
Pantothenic acid (mg)			2.21	0.43	2.64
Riboflavin (mg)		0.11	2.11	0.04	2.25
Thiamin (mg)			0.40	0.14	0.53
Vitamin A (RAE) (µg)	0.92		1050.34		1051.26
Vitamin B-6 (mg)			1.00	0.08	1.08
Vitamin B-12 (µg)			2.63		2.63
Vitamin C (mg)			79.01		79.01
Vitamin D (µg)			10.54		10.54
Vitamin E (µg)			12.12	4.44	16.55
Vitamin K (µg)				14.60	14.60
Anti-Nutrient					
Phytic acid (g)					0.21

[1] MAM, moderate acute malnutrition; RUSF, ready-to-use supplementary food; WPC80, whey protein concentrate with 80% protein.

Supplemental Table 3. Results of acceptability testing of the two RUSF products (mean +/- SD)[1]

	Soy RUSF (n = 29)	**Whey RUSF** (n = 30)
Observed time to complete eating (min)	7:17 ± 3:50	7:14 ± 3:34
Day 1 child liking of RUSF (1-5 scale)	4.59 ± 0.82	4.57 ± 0.73
Day 1 caregiver liking of RUSF (1-5 scale)	4.72 ± 0.65	4.87 ± 0.43
Day 4 child liking of RUSF (1-5 scale)	5.00 ± 0.00	4.97 ± 0.18
Reported no difficulty consuming food over 4 d (n (%))	26 (90)	28 (93)

[1] Values are mean ± SDs or n (%). RUSF, ready-to-use supplementary food.

Supplemental Table 4. Frequency of dairy product consumption at enrollment among children treated for MAM[1]

	Soy RUSF					Whey RUSF				
	Never	**1-2x per yr**	**1-2x per mo**	**1-3x per wk**	**1-2x per d**	**Never**	**1-2x per yr**	**1-2x per mo**	**1-3x per wk**	**1-2x per d**
Cow's milk	780 (84.2)	53 (5.7)	40 (4.3)	37 (4.0)	16 (1.7)	835 (85.6)	47 (4.8)	41 (4.2)	36 (3.7)	16 (1.6)
Goat's milk	875 (94.5)	20 (2.2)	17 (1.8)	8 (0.9)	4 (0.4)	923 (94.7)	26 (2.7)	8 (0.8)	11 (1.1)	5 (0.5)
Milk powder	796 (86.0)	50 (5.4)	40 (4.3)	23 (2.5)	13 (1.4)	851 (87.3)	52 (5.3)	36 (3.7)	28 (2.9)	8 (0.8)
Cow's butter	908 (98.1)	6 (0.6)	5 (0.5)	3 (0.3)	1 (0.1)	964 (98.9)	6 (0.6)	4 (0.4)	2 (0.2)	1 (0.1)
Butter spread	882 (95.2)	18 (1.9)	12 (1.3)	9 (1.0)	4 (0.4)	936 (96.0)	17 (1.7)	12 (1.2)	6 (0.6)	3 (0.3)
Yogurt	872 (94.2)	23 (2.5)	15 (1.6)	11 (1.2)	3 (0.3)	910 (93.3)	27 (2.8)	12 (1.2)	16 (1.6)	8 (0.8)

[1] Values are mean ± SDs. MAM, moderate acute malnutrition; RUSF, ready-to-use supplementary food.

Supplemental Table 5. Amino acid content of intervention foods, based on a typical daily ration (105.4 g) for a child with MAM weighing 7 kg[1]

	Soy RUSF	**Whey RUSF**
Protein Digestibility-Corrected Amino Acid Score (PDCAAS)	0.78	1.00[2]
Digestible Indispensable Amino Acid Score (DIAAS)	0.74	0.72
Aromatic amino acids [g (% total amino acids)]	2.13 (12.5)	1.32 (12.2)
Histidine (g)	0.44	0.25
Phenylalanine (g)	0.88	0.49
Tryptophan (g)	0.19	0.17
Tyrosine (g)	0.63	0.41
Branched-chain amino acids [g (% total amino acids)]	2.73 (16.0)	1.79 (16.5)
Isoleucine (g)	0.69	0.47
Leucine (g)	1.27	0.82
Valine (g)	0.76	0.50
Sulfur-containing amino acids [g (% total amino acids)]	0.39 (2.3)	0.43 (4.0)
Cysteine (g)	0.19	0.22
Methionine (g)	0.20	0.21
Other amino acids [g (% total amino acids)]	11.81 (69.2)	7.30 (67.3)
Alanine (g)	0.72	0.44
Arginine (g)	1.67	0.97
Aspartic acid (g)	2.05	1.25
Glutamic acid (g)	3.35	2.09
Glycine (g)	0.82	0.50
Lysine (g)	0.89	0.57
Proline (g)	0.81	0.51
Serine (g)	0.87	0.49
Threonine (g)	0.63	0.48

[1] MAM, moderate acute malnutrition; RUSF, ready-to-use supplementary food.
[2] Standard PDCAAS score is truncated at 1.00, but full calculation is 1.2.

Addendum 1. Additional cost-effectiveness results not included in the published article that comprises Chapter 1

Cost-effectiveness comparing whey and soy RUSF in Chapter 1

The cost-effectiveness analysis regarding the use of whey RUSF versus soy RUSF involved calculating two cost-effectiveness ratios: 1) the cost of each food product per child recovered, and 2) the cost of each food product plus operation costs of the SFP per child recovered. Other costs that were not collected in this study (e.g. costs associated with handling, distributing, and consumption of the foods) were identical across the two different types of food.

Cost to produce the food was $2.78/kg and $3.13/kg for soy and whey RUSF, respectively. The food cost per child recovered was $11.96 and $10.56 for whey and soy RUSF, respectively. Therefore, when considering only the cost of food in the treatment of MAM, the soy RUSF was more cost-effective because whey RUSF cost $1.40 more per child recovered than the soy RUSF.

However, when taking into account total SFP operating costs in addition to food costs, the cost per child recovered was $54.34 and $54.76 for whey and soy RUSF, respectively. Therefore, when including operational costs, whey RUSF was more cost-effective, as it was $0.42 less expensive per child recovered than soy RUSF. In a hypothetical scenario with a given budget of $50,000 for total operations and food costs, using whey RUSF (as opposed to soy RUSF) would result in 3 more kids recovered. These results show that using whey RUSF in the context of the current study is more cost-effective than using soy RUSF to treat children with MAM. It is important, however, to recognize that operational costs will vary greatly in other contexts, which may change the final cost-effectiveness ratios.

Addendum 2. Additional detailed costing and cost-effectiveness calculations for Whey and Soy RUSF

Cost of Food Production

The following outlines the procedure of collecting total costs for local production of RUSF and RUTF. *Full price breakdown for each food on the following pages.*

Food Raw Material:
- Contacted suppliers of overseas materials for current $ per kg
- Contacted Factory Manager for current $ per kg of local materials
- Contacted Starship Int'l (international shipping company) to receive quotes for overseas shipping
- For orders placed in 2015, some prices were provided by BPP employees that had supplier invoices for the orders for a current $ per kg

Import/Duties:
- Importation taxes/duties were reported by Factory Manager in Malawi

Production Amounts:
- All production amounts were verified with Production Manager in Malawi to ultimately calculate a cost per kg of finished product (including operating/overhead costs)

Packaging:
- In order for the foods to be more comparable, the price per finished product includes the same packaging type for all three foods: foil sachets (as required by international buyers)
- The Factory Manager confirmed that producing the different food types on the same machinery line with the same packaging was feasible and would result in the same production rate.
- Keeping same packaging puts the comparison more on the actual food ingredients – the focus of the study.

Factory Operating Costs:
- Factory Manager provided monthly and annual costs to run factory
- Combined this information with production rate to get a $ per kg of operating cost
- Storage costs were included in overall operating costs—since packaging is the same across foods, then storage costs is the same across foods.

Product Testing:
- Contacted Silliker Lab in the US to receive a current price quote for batch testing of both RUSF (tests as required by WFP) and RUTF (tests as required by UNICEF)… which didn't differ much
- Factory Manager provided the cost to send samples to lab for batch testing

Currency and Conversion:
- All price quotes were gathered as 2015 price quotes
- All Malawian Kwacha were converted to USD, (1 MWK = 0.00183 USD according to Online Currency Converter: Oanda.com, rate as of 20 Aug 2015)

Results:

Soy RUSF = $2.78; **Whey RUSF = $3.13**; **RUTF = $4.82** per kg of finished product

Cost of <u>Soy RUSF</u> per kg

	KG per mix (200kg of finished product)	price per kg Raw Material Cost (USD)	price per kg Shipping Cost (USD)	Total Cost Before Tax (USD)	Tax & Duties (USD)	Total Cost (USD)
Extruded soymeal	48.0	$0.64		$30.74		$30.74
Sugar	51.4	$0.92		$47.10		$47.10
Palm Oil	19.0	$1.01		$19.12		$19.12
Soy Oil	14.6	$1.05		$15.36		$15.36
Peanut Paste	53.8	$1.85		$99.68		$99.68
Soy Premix (FT127271)	9.2	$7.64	$2.44	$92.72	20%	$111.27
T-180 Emulsifier	4.0	$0.61	$1.16	$7.09	30%	$9.21
package: Foils (price of raw material includes shipping)	1950	$0.01		$27.08	50%	$40.62
package: Carton	13	$0.72		$9.40		$9.40
package: Sleeves	13	$0.04		$0.48		$0.48
package: Bailers	13	$0.11		$1.48		$1.48
package: Cellotape	0.026	$45.75		$1.19		$1.19
raw materials costs (per mix)						$385.67
operating costs (per mix)						$149.15
testing costs (per mix)						$20.37
TOTAL costs (per mix = 200kg)						$555.19
TOTAL costs (per kg)						**$2.78**

Cost of Whey RUSF per kg

	KG per mix (200kg of finished product)	price per kg Raw Material Cost (USD)	price per kg Shipping Cost (USD)	Total Cost Before Tax (USD)	Tax & Duties (USD)	Total Cost (USD)
WPC 80 (Davisco WPC 80)	9.8	$1.36	$1.68	$29.77	20%	$35.73
Whey Permeate (Arla Variolac 850)	37.4	$0.50	$2.18	$99.95	20%	$119.94
Sugar	48.8	$0.92		$44.72		$44.72
Palm Oil	19	$1.01		$19.12		$19.12
Soy Oil	15.2	$1.05		$15.99		$15.99
Peanut Paste	58.8	$1.85		$108.95		$108.95
Custom Premix Whey(FT 126476)	7	$7.78	$2.44	$71.53	20%	$85.84
T-180 Emulsifier	4	$0.61	$1.16	$7.09	30%	$9.21
package: Foils (price of raw material includes shipping)	1950	$0.01		$27.08	50%	$40.62
package: Carton	13	$0.72		$9.40		$9.40
package: Sleeves	13	$0.04		$0.48		$0.48
package: Bailers	13	$0.11		$1.48		$1.48
package: Cellotape	0.026	$45.75		$1.19		$1.19
raw materials costs (per mix)						$456.94
operating costs (per mix)						$149.15
testing costs (per mix)						$20.37
TOTAL costs (per mix = 200kg)						$626.47
TOTAL costs (per kg)						**$3.13**

Cost Effectiveness Ratios of Whey and Soy RUSF

Cost-effectiveness ratios (C-E ratios) are defined by the cost of each food product per outcome (child recovered). The following is a breakdown of the food cost per child treated (whey and soy RUSF) and food cost per child recovered (whey RUSF and soy RUSF). The following is a procedure for calculating C-E ratios:

1. **Determined the total amount of food dosed in the treatment of an average MAM child** (average weight of child and average number of days on treatment were based on study data)

Food Dosing per Child Treated		
Dosing = 75 kcal / kg body wt / days of treatment*	whey	soy
Kcal Needed (per weight, per day)	75	75
Average wt per child	7.143579	7.138814
Average # of days	29.30	30.38
Average kcal dose per child	**15,698.01**	**16,265.79**

**This dosing is approximate. As noted below, the kcal/g are different per food. Yet in order to keep participants blinded, both foods were packaged in the same bottle sizes. If the dosing according to total weight did not equal a whole number of bottles, rather than providing only a portion of a bottle of food, the total amount provided was rounded up to the next whole bottle. Therefore, the dosing was not exactly precise to the above calculation.*

2. **Determined average food cost to treat one child** (based on an average child weight of 7.14 kg and receiving food for 29.3 days in whey group and 30.48 days in soy group)

Average Food Costs per Child Treated	kcal/g in food	Average kcal dosed per kid:	Ave g of food dosed per kid:	Ave kg of food dosed per kid	Price per kg of food	**Food cost per child**
Whey RUSF	4.90	15,698.01	3,202.87	3.20	$3.13	**$10.03**
Soy RUSF	5.31	16,265.79	3,062.69	3.06	$2.78	**$8.50**

3. **Determined average food cost per child recovered**:
   a. Food cost per child x total number of children treated = total cost to treat all children
   b. Total cost to treat all children ÷ number of children recovered = cost per child recovered

Food Cost per Child Recovered in Study	**Whey RUSF**	**Soy RUSF**
Food Cost per child treated:	$10.03	$8.50
Total number of children treated in study	1144	1086
Total Food Costs for all children treated in study	$11,477.10	$9,233.01
Number of children recovered in study	960	874
C-E Ratio: ($ of food per child recovered)	**$11.96**	**$10.56**

Cost-Effectiveness Results (food costs)

The food costs per child recovered use whey RUSF = $11.96
The food costs per child recovered using soy RUSF = $10.56

Cost Effectiveness Ratios including SFP Program Costs:

The following cost-effectiveness ratios are defined by the cost of each food product *and* SFP operating costs per outcome (child recovered). SFP operating costs were calculated based on St. Louis Nutrition Project costs associated with running 21 children's SFP programs in Malawi. *These are fully listed on the following page.*

The following is the procedure for the collection and determination of the SFP program costs:

SFP Program Costs:

- Operational costs include the following components:
  - Personnel Salaries (Office Manager, Program Manager, 2 Expat Volunteers, Drivers, Nurses, and Community Health Workers)
  - Office/Compound Costs (Compound/Office Rent, upkeep costs, 2 Houseworkers' salary, office supplies, and communication costs)
  - Program supplies (height boards, muac tapes, scales, etc.)
  - Travel Costs (fuel, car maintenance, COF license, car insurance)
  - Capital costs (annuitization of 11 vehicles, using average price of cars, with the assumption that useful life = 10 years, estimated 53% direct use for SFP clinics)
- Sources for costs included:
  - Monthly expense reports as provided by Office Manager
  - Nurse Salaries as provided by College of Medicine in Malawi
  - Interview and email exchanges with Office Manager for remaining items (prices of cars, overhead/rent, etc.)
- % Usage specifically for SFP operations
  - Many line items represented the total annual cost for SFP operations and other things (such as research operations, maternal SFP clinics, etc.)
  - For these line items, a percentage was chosen to represent the line item cost that went directly towards children SFP operations
  - Percentages were determined by: personal observation, evaluation of purchasing patterns via expense reports, and number of children MAM SFP clinics out of the total SFP clinics

Currency and Conversion:

- All prices quotes were gathered as 2015 prices (from 2015 expense reports, salary reports, etc.)
- All Malawian Kwacha were converted to USD, (1 MWK = 0.00183 USD according to Online Currency Converter: Oanda.com, rate as of 20 Aug 2015)

Total Costs to treat children:

- All costs were based on one year of operating SFP clinics
- Total number of MAM children treated over the course of 1 year (May 2014 – May 2015)

SFP Operating Cost per Child	
Total SLNP SFP Operating Costs:	$133,903.08
Total MAM (study & non-study) children treated:	3,765
Total Operating Cost per Child:	$35.57

Operating Costs			
Personnel	**Source**	**Notes**	**USD (Annual)**
Office Manager	Office Manager	estimated 30% for MAM clinic, per month * 12	$5,112.76
Program Manager (expat)	Program Manager	Annual	$25,000.00
2 Volunteers (expat)	Office Manager	$100 per week * 52	$10,400.00
2 Drivers	Office Manager	estimated 53% for MAM clinic, per month * 12	$6,093.74
3 Nurses	Scientific Admin.	estimated 53% for MAM clinic, per month * 12	$8,749.72
Staff Daily Stipends	Expense Report	estimated 53% directly for MAM clinic, per month * 12	$12,181.77
CWHs/Volunteers	Program Manager	21 clinics, 5 CHW @ 1500, 2 vols @ 1000 - every two weeks	$8,762.04
Office/Compound	**Source**	**Notes**	
Compound/Office Rent	Office Manager	estimated 25% for MAM clinic, per 6 month * 2	$3,486.15
Upkeep & other compound	Expense Report	estimated 25% for MAM clinic, per month * 12	$546.48
House worker: I	Office Manager	estimated 25% for MAM clinic, per month * 12	$731.35
House worker: II	Office Manager	estimated 25% for MAM clinic, per month * 12	$439.20
Office Supplies	**Source**	**Notes**	
internet	Office Manager	estimated 25% directly for MAM clinic, per month * 12	$400.77
printer ink	Office Manager	estimated 15% directly for MAM clinic, per month * 12,	$312.93
computers/comp software	estimation	1 computer @ $700, annuitized by 5 yrs	$140.00
printer	estimation	1 printer @ 68,700 MKW, annuitized by 5 yrs	$25.14
misc. supplies (copying, etc.)	Expense Report	estimated 15% directly for MAM clinic, per month * 12,	$3,120.78
Communication (phones, etc.)	Expense Report	estimated 40% directly for MAM clinic, per month * 12	$1,035.72
Program supplies	**Source**	**Notes**	
height boards	Data Analyst	$219/board; need 3 for operations; replace 1 a year	$219.00
muac tapes	Data Analyst	$299/scale; need 3 for operations; replace 1 a year	$299.00
scales	Data Analyst	$358.54/1000 MUACs, need about 500 new each year	$179.27
(jumbos, spoons, dettol, etc.)	Expense Report	estimated 10% "study supplies" for non-research MAM	$7,571.03
miscellaneous costs	Expense Report	estimated 30% for MAM clinic, per month * 12	$1,147.97
Travel Costs	**Source**	**Notes**	
Fuel	Expense Report	estimated 53% directly for MAM clinic, per month * 12	$13,396.34
Car maintenance	Expense Report	estimated 53% directly for MAM clinic, per month * 12	$18,823.06
COF license	Office Manager	18000 per car, per year (11 cars)	$362.34
Insurance	Office Manager	52425 per car, per year (11 cars)	$1,055.32
Capital Costs			
Vehicles	**Source**	**Notes**	
11 vehicles	Office Manager/ estimation/ annuitization	average price of car, assumption that useful life = 10, annuitization, estimated 53% directly for MAM clinic use	$4,311.21
Total SLNP Annual Operating Costs (estimated for MAM clinic operations)			**$133,903.08**

The following is the total cost (including both food cost and SFP operations costs) per child treated:

Total Cost per Child Treated (Food + SFP Operations)				
	Whey RUSF		**Soy RUSF**	
	USD	*%*	USD	*%*
SLNP SFP Operating Costs	$35.57	*78%*	$35.57	*81%*
Food Cost	$10.03	*22%*	$8.50	*19%*
Total Cost per child treated	**$45.60**		**$44.07**	

The following is the C-E ratio for total cost (including both food costs and SFP operations costs) per child recovered.

Cost per Child Recovered in Study (Food + SFP Operations)		
	Whey RUSF	**Soy RUSF**
Cost per child treated:	$45.60	$44.07
Total number of children treated in study	1144	1086
Total Costs for all children treated in study	$52,163.72	$47,856.85
Number of children recovered in study	960	874
C-E Ratio: ($ per child recovered) (Food + SFP Operations)	**$54.34**	**$54.76**

<u>Cost-Effectiveness Results (food and SFP operations costs)</u>

The costs (food + SFP) per child recovered using whey RUSF = $54.34
The costs (food + SFP) per child recovered using soy RUSF = $54.76

The following is a comparison of how many children could be treated and recovered using the two foods given a total budget of $50,000.

Comparison of how many children can be treated using each food given a total budget of $50,000.		
	Treated	**Recovered**
Whey RUSF	1,097	922
Soy RUSF	1,135	919
Difference using Whey RUSF instead of Soy RUSF	38 <u>less</u> kids treated using Whey RUSF	3 <u>more</u> kids recovered using Whey RUSF

<u>Conclusion:</u>
When taking into account operational costs, the total cost difference between the two foods is $0.42 less per child recovered when using the Whey RUSF. This represents a 0.8% decrease in total costs per child recovered. Given a total budget of $50,000, the use of whey RUSF instead of soy RUSF would results in 3 more children recovered.

Addendum 3. Additional discussion regarding protein quality of the Whey and Soy RUSFs

Just as the amount of protein in food provided to children with MAM is important, the quality of protein is also critical to facilitate recovery. Animal-sourced foods typically contain a higher quality protein than plant-sourced foods. This also holds true when comparing whey and soy in supplementary foods provided to children with MAM. A review of whey in fortified blended foods for vulnerable groups by Hoppe et al. (30) in 2008 shows that adding whey in fortified blended foods would improve the overall protein quality of MAM treatment foods, which could have potential metabolic advantages. Whey protein is particularly high in sulfur-containing amino acids and is also an excellent source for branched-chain amino acids, which are metabolized by muscle and counteract lean tissue breakdown.

The two most commonly used methods for measuring protein quality are the Protein Digestibility-Corrected Amino Acid Score (PDCAAS) and the Digestible Indispensable Amino Acid Score (DIAAS). The PDCAAS score is based on the ratio of the amount of the first-limiting amino acid to the amino acid requirement of a child between the ages of 1 and 2 years old. The amino acids are corrected for protein digestibility based on fecal nitrogen digestibility in rats. Any PDCAAS values that exceed 1 are truncated to 1. In 2011, the Food and Agriculture Organization recommended the use of the DIAAS over the PDCAAS when measuring protein quality. The DIAAS is based on true ileal amino acid digestibility for each amino acid individually for food ingredients, without truncating scores. The DIAAS is preferred over the PDCAAS as ileal estimates of protein digestibility are more accurate than fecal digestibility estimates, amino acid digestibility values are more accurate than protein digestibility values, and the DIAAS scores are not truncated.

As outlined in **Supplemental Table 5**, the PDCAAS is 1.00 and 0.78 for the whey and soy RUSF, respectively. The DIAAS is 0.72 and 0.74 for the whey and soy RUSF, respectively. The difference in scores is most likely due to the difference in limiting amino acids and digestibilites used to calculate the scores. While the PDCAAS is higher in the whey RUSF, the DIAASs are nearly identical across both foods. The DIAAS is likely the more accurate means for comparing the two foods' protein quality. Because the protein quality is so similar between the two foods (and even slightly lower for the whey RUSF), it is unlikely that this played a significant role in the superior recovery and growth outcomes observed in the children who received the whey RUSF.

Chapter 2. A package of basic health and nutrition interventions provided in addition to a supplementary feeding program improves the long-term recovery of children with moderate acute malnutrition: a cluster randomized controlled clinical trial

Abstract

Background: Children who recover from moderate acute malnutrition (MAM) have high rates of relapse back into acute malnutrition in the year following nutritional recovery. Interventions to decrease these adverse outcomes are needed to maximize the overall effectiveness of supplemental feeding programs (SFP).

Objective: We evaluated the effectiveness of a package of health and nutrition interventions on improving the proportion of children who sustained recovery without relapse for one year following treatment for MAM.

Design: We conducted a cluster randomized controlled clinical effectiveness trial involving rural Malawian children 6-62 months old enrolled upon discharge from an SFP for MAM. The intervention group received a package of health and nutrition interventions in addition to routine health and nutrition counseling. The package of interventions consisted of a lipid nutrient supplement (LNS), deworming medication, zinc supplementation, a bed net, and malaria chemoprophylaxis. Logistic regression was used to determine impact of the intervention as well as to identify factors associated with sustained recovery.

Results: The proportion of children that sustained recovery was higher in the intervention group throughout the 12-month follow-up period: 69% vs. 63% ($P < 0.05$) at three months, 64% vs. 59% ($P < 0.05$) at six months, and 53% vs. 48% ($P < 0.1$) at 12 months after enrollment for the intervention and control groups, respectively. When controlling for other factors in a logistic regression model, the strongest predictors of sustained recovery were larger MUAC upon SFP admission (OR=1.19, 95% CI: 1.15-1.22, $P < 0.001$), greater MUAC change between SFP admission and discharge (OR=5.80, 95% CI: 3.05-11.03, $P < 0.001$), and higher WHZ score upon discharge (OR=2.70, 95% CI: 1.87-3.91, $P < 0.001$).

Conclusion: The provision of a package of basic health and nutrition services in addition to traditional SFP treatment improves the long-term nutritional status of children recovering from MAM.

Introduction

Children with moderate acute malnutrition (MAM) are generally treated for several weeks in a community-based supplementary feeding program (SFP) that provides one of a variety of supplementary foods (1). Children are generally discharged from SFPs as recovered after achieving an anthropometric threshold based on mid-upper arm circumference (MUAC) or weight-for-height Z-score (WHZ) or after receiving food for a fixed duration of time (2).

Studies that have systematically followed children after discharge find that relapse back to MAM, the development of severe acute malnutrition (SAM), and other poor outcomes are common (3-7). A study in Niger followed children who were successfully discharged from SFP for six months and found that 20% of children relapsed during that time (6). A study in Malawi found only 63% of children successfully treated for MAM sustained recovery for 12 months (4). Other studies also demonstrate high relapse rates among children discharged after treatment for severe acute malnutrition (SAM) (3, 5). A more recent study from Burkina Faso of a mixed population of children (90% MAM and 10% SAM) reported relapse rates closer to 15%, although more than a third of those children were lost to follow-up, suggesting possibly an even higher rate of relapse or death (7).

In addition to high relapse rates, almost all studies report that common childhood illnesses are prevalent among those who relapse or die after initial recovery (3, 4). Illnesses, such as fever, cough, malaria, and diarrhea, are frequently present during the initial three months after discharge (when relapse rates are the highest), then decrease thereafter (3). This suggests that the same common infectious diseases that often afflict children in resource limited settings (8) may be associated with relapses in children recovering from acute malnutrition.

In this study, we assessed whether a package of simple and affordable health and nutrition interventions added after achieving anthropometric criteria for recovery from MAM could improve the proportion of children who sustained recovery for one year following treatment.

Subjects and Methods

Subjects and Setting

Children aged 6-62 months who had recovered from MAM, as defined by a MUAC $\geq$ 12.5 cm without bipedal edema (9), were recruited from 21 rural SFP clinics in southern Malawi from April 2014 to June 2015. Children were excluded if they had a chronic debilitating illness, or had a history of peanut, milk, or soy allergy. Children were also excluded if they had received therapy for acute malnutrition within one month prior to admission into the SFP, in order to focus on the sustained recovery from an initial discrete episode of MAM. Those whose MUAC dropped below 11.5 cm or who developed edema during initial treatment for MAM were also excluded from the study, as they were considered to have progressed to SAM and were treated as such.

The study communities predominantly consist of impoverished subsistence farming families living in mud and thatch homes. Maize is the staple crop in the region and gathered once a year following a single rainy season that stretches from December to March annually; this season is also notable for high rates of diarrhea, malaria, and other acute infectious diseases, along with a significant increase in food insecurity and rates of acute malnutrition.

Study Design

The study was a cluster randomized, controlled clinical effectiveness trial. Randomization was performed across clinic sites, rather than at the individual level to minimize the risk of sharing and cross contamination. The primary outcome was the proportion of children who sustained recovery, defined as maintaining MUAC $\geq$ 12.5 cm without bipedal edema, for 12 months following initial recovery from MAM.

Participants and field researchers were not blinded to the allocation of groups, as it was inherently evident whether or not children received the package of interventions. However, after each child's anthropometric and clinical data were entered into the computer database, the group allocation was blinded during statistical analyses. Unblinding did not occur until after the end of the trial and after all statistical analyses had been completed.

When calculating sample size, a correction factor was used to adjust for any implementation or population differences among sites. An intracluster correlation coefficient (ICC) of 0.007 and a coefficient of variation of cluster size of 0.65 were calculated from pilot data and similar studies conducted previously at the same study sites (2, 4). A power of 80% and alpha of 0.05 were used to identify a sample size sufficient to detect a 10 percentage point difference in the proportion of children that sustained recovery between the control and intervention groups. Estimating that 63% of children would sustain recovery for 12 months without any additional interventions (4), a minimum average of 58 participants per cluster was calculated to be necessary across the 21 clusters. Sample size was calculated using Stata Version 13.0 (StataCorp LP, College Station, TX). Additional enrollments were planned to account for the possibility of a high lost to follow-up rate.

To identify if an association existed between immune function and sustained recovery following treatment for MAM, serum complement C3 (as a proxy for immune recovery (10)) was measured in a random sample of 145 children at the time of SFP discharge and four weeks later. Whole blood was drawn into heparinized tube and kept cold in an insulated plastic box with freezer packs in the field. Immediately upon returning from field clinics, the blood was centrifuged to isolate the plasma, which was frozen at -80°C. Samples were transferred while frozen to the Core Laboratory at St. Louis Children's Hospital for analysis of serum complement C3 levels (Roche Cobas, Indianapolis, IN).

Intervention

The control group received nutrition counseling at the point of discharge from SFP, consisting of messages regarding proper complementary feeding, caretaker recognition of common childhood illnesses, and appropriate health-seeking behaviors. The treatment group received the same counseling plus five additional components that made up the intervention package:

1. 40 g/d of a lipid-based nutrient supplement (LNS) providing 200 kcal and one Recommended Dietary Allowance (RDA) of almost all micronutrients for 8 weeks upon discharge from SFP (**Table 1**). The LNS consisted of 28% peanut paste, 18% non-fat dry skimmed milk powder, 24.5% palm oil, 21.2% sugar, 6.8% custom micronutrient mix, and 1.5% emulsifier.
2. A single dose of albendazole (200 mg for < 2 years old and 400 mg for ≥ 2 years old) for deworming at the time of discharge from SFP.
3. 14-day course of 20 mg zinc sulfate starting at the time of discharge from SFP. The dose used here is the same as recommended after an episode of diarrhea and has also been shown to decrease the progression of environmental enteric dysfunction (11).
4. A single insecticide-treated bed net at the time of SFP discharge to reduce the risk of malaria.
5. Sulfadoxine-pyrimethamine for malaria chemoprophylaxis (12) at a dose of approximately 25 mg/kg (sulfadoxine component) monthly during the peak of the rainy season (December-February), as most adverse outcomes in children who recover from MAM occur during this time (4).

These interventions have all individually been proven safe, effective, and affordable in this context to improve the overall health of children, but are often not universally implemented due to resource and logistical limitations. The package was thus provided specifically to this high-risk population to increase the likelihood of sustaining recovery, especially during the first few months after discharge from SFP and throughout the rainy season when malaria and relapse are most common.

Subject Participation

After enrollment criteria were confirmed, informed consent was obtained from all caregivers. Information on demographic characteristics, health history, and household food insecurity was collected. Health history questions included caregiver-observed illness symptoms during the prior two weeks, immunization status, use of any nutritional supplements, use of malaria prophylaxis, timing of most recent deworming, and use of a bed net. Household food security was assessed using the validated, nine-item Household Food Insecurity Access Scale (HFIAS) (13). At enrollment and each subsequent visit, nutrition researchers and senior pediatric nurses conducted standard anthropometric measurements and assessed other clinical conditions. Weight was measured using an electronic scale to the nearest 5 g; length was measured using a rigid length board to the nearest 0.1 cm; and MUAC was measured with a standard insertion tape to the nearest 0.1 cm. Edematous malnutrition (kwashiorkor) was assessed by examining for bilateral pitting edema.

All caregivers were asked to return to the clinic for subsequent follow-up visits at 1, 3, 6, and 12 months after enrollment. Additional monthly visits were scheduled for all children during the height of the rainy season (December to February), where malaria prophylaxis was also provided at the intervention sites. Caregivers were also educated that they could bring their children for additional evaluations at any time during the course of the follow-up study if they were concerned about their child's nutritional status or if a community health worker had referred them. If at any point during the follow-up period a child was identified as being malnourished, s/he received the appropriate RUTF or RUSF ration and treated until the child reached anthropometric recovery.

At the end of the 12-month follow-up period, each child was classified as having "sustained recovery," defined as having MUAC ≥ 12.5 cm at every follow-up visit for 12 months; "relapsed to MAM," defined as MUAC of 11.5-12.4 cm at any point during the follow-up period; "developed SAM," defined as MUAC < 11.5 cm and/or bipedal edema (kwashiorkor) at any point during the follow-up period; "died"; or "lost to follow-up (LTFU)," defined as defaulting on a scheduled visit and never returning. Poor outcomes included relapsing to MAM, developing SAM, death, or LTFU. If a child experienced two or more poor outcomes over the course of the follow-up period, the most severe category was assigned as the final outcome.

Ethical Approval

The study was approved by the University of Malawi's College of Medicine Research and Ethics Committee, Washington University's Human Research Protection Office, and Tufts University's Internal Review Board. Permission to conduct the study was obtained by each site's District Health Officer and/or District Nutritionist.

Statistical Analyses

All data were double entered into an Access (Microsoft Corp., Redmond WA) database and verified against original paper data forms when discrepancies were identified. Anthropometric indices were based on the World Health Organization's (WHO) 2006 Child Growth Standards (14), calculated using the WHO Anthro software (WHO, Geneva). Rates of MUAC and length gain were calculated in mm/d and weight gain was calculated in g/kg/day. Dichotomous outcomes were compared using either Fisher's exact or chi-squared test, while the Student t-test was used for comparing continuous variables. Correction factors were included to account for clustering at the health clinic level. P-values less than 0.05 were considered statistically significant.

Binary logistic regression models with cluster adjusted robust standard errors were used to determine if the intervention had a statistically significant impact on the outcomes and identify other clinical factors associated with sustained recovery. Models were constructed using backward elimination, whereby all anticipated covariates were initially included and dropped if they were not statistically significant at $P < 0.05$. All statistical analyses were conducted using Stata Version 13.0 (StataCorp LP, College Station, TX).

Results

Between April 2014 and June 2015, 1497 children recovered from MAM at 21 SFP study clinics and were enrolled in the study. During analysis, ten children were excluded due to failure to meet enrollment criteria, leaving 1487 for the final analysis, with 718 children at 10 control sites and 769 children at 11 intervention sites (**Figure 1**).

A few characteristics differed between the control and intervention groups, which were later controlled for in the regression models (**Table 2**).

Of the 1487 children included in the final analysis, 754 (51%) sustained recovery for all visits during the 12-month follow-up period, while 541 (36%) relapsed to MAM, 73 (5%) developed SAM, 15 (1%) died, and 104 (7%) were LTFU (**Table 3**). Many children experienced multiple relapses: of those who relapsed to MAM only, 26%, 10%, and 5% relapsed twice, three times, and four or more times, respectively. Additionally, of those who developed SAM, 69% also relapsed to MAM at least once. Those who relapsed to MAM multiple times required longer treatment for those relapses during the follow-up period than those who relapsed only once ($P < 0.001$). Furthermore, MUAC dropped significantly lower among those who relapsed to MAM multiple times compared to those who relapsed only once ($P < 0.001$). Approximately half of all relapses (to either MAM or SAM) occurred within the first three months of initial recovery from MAM (**Figure 2**).

The proportion of children that sustained recovery was higher in the intervention group throughout the follow-up period: 604 (78%) vs. 531 (75%) at one month ($P < 0.05$); 530 (69%) vs. 455 (63%) at three months ($P < 0.05$); 491 (64%) vs. 421 (59%) at six months ($P < 0.05$); and 407 (53%) vs. 347 (48%) at 12 months ($P < 0.1$) for the intervention and control groups, respectively (Table 3). Secondary outcomes, including linear growth and illness during the 12-month follow-up period, were similar across both intervention and control groups. The intervention package, which included a bed net and malaria chemoprophylaxis during the rainy season, did not result in a significant reduction of relapse rates during the rainy season: 547 (71%) vs. 487 (68%) sustained recovery during the rainy season (*P* = 0.167); 156 (20%) vs. 148 (21%) relapsed to MAM (*P* = 0.876); and 7 (1%) vs. 13 (2%) developed SAM (*P* = 0.132) for the intervention and control groups, respectively.

When controlling for baseline characteristics in logistic regression modeling, children who received the intervention were more likely to sustain recovery throughout the follow-up period than those who did not (OR=1.40, 95% CI: 1.06-1.85, *P* < 0.05) (**Table 4**). The strongest predictors of sustaining recovery were: having larger MUAC upon SFP admission (OR=1.19, 95% CI: 1.15-1.22, *P* < 0.001), greater MUAC change between SFP admission and discharge (OR=5.80, 95% CI: 3.05-11.03, *P* < 0.001), and higher SFP discharge WHZ score (OR=2.70, 95% CI: 1.87-3.91, *P* < 0.001). Having a larger MUAC upon SFP discharge was predictive of sustained recovery for three months (OR=1.14, 95% CI: 1.06-1.23, *P* = 0.001) and six months (OR=1.10, 95% CI: 1.05-1.15, *P* < 0.001), but not at 12 months. Other factors, including receiving RUTF as opposed to RUSF during initial SFP, shorter time to recovery during initial SFP, greater weight gain during initial SFP, and use of nutritional supplements prior to initial SFP were associated with sustained recovery in univariate analysis (**Supplemental Table 1**), but were not significantly associated with sustained recovery after controlling for other variables.

Out of the 145 children who provided blood samples taken at the time of SFP discharge and one month following discharge, nearly all (96%) serum complement C3 levels were within the normal range (80-160 mg/dL).

Discussion

In this cluster randomized controlled clinical trial, we demonstrate that providing a package of basic health and nutrition interventions to children who recover from MAM increases the proportion of children who sustain recovery during one year of follow-up.

Despite the positive impact of the intervention, only 53% of children who received the intervention sustained recovery from MAM for one year following SFP treatment. Our analysis revealed a diversity of poor outcomes among those who did not sustain recovery. Some children experienced one short, mild episode of moderate malnutrition and quickly recovered after re-enrollment in SFP to remain free from moderate or severe acute malnutrition thereafter. Others relapsed multiple times with more severe episodes of acute malnutrition requiring longer treatment. These vastly different health trajectories highlight that even though children in SFPs are all classified with the same type and severity of malnutrition (*i.e.,* MAM), not all children with MAM are at the same risk for poor short and long term outcomes. This suggests that a uniform approach for treating all children with MAM may not be best for ensuring that all reach sustained recovery.

Several factors associated with sustained recovery from MAM were identified that may provide insight for future interventions to reduce relapse. The strongest predictors of sustained recovery consisted of having superior anthropometric measurements during SFP treatment, such as a larger MUAC upon admission. For every one-millimeter increase in MUAC upon admission to the SFP, a child has 19% higher odds of sustaining recovery for a year following treatment. These results are consistent with previous findings that the severity of malnutrition at admission to feeding programs is linked to increased risk for mortality and relapse among children following SAM (5) and MAM treatment (2, 4). While most SFP protocols provide the same treatment to children with MAM regardless of MUAC, our results suggest establishing routine follow-up procedures for children with lower MUAC upon admission and discharge, given their increased risk for poorer long-term outcomes. Routine follow-up after discharge may help catch relapses to MAM earlier, before they progress to SAM or die.

Higher discharge MUAC and WHZ were also associated with sustained recovery for 6 -12 months following SFP discharge. In a similar observational study, results showed that higher discharge MUAC and WHZ were more important than duration of treatment in achieving sustained recovery (2). Our findings here corroborate the potential benefit of treating children with MAM to a higher anthropometric target than the current MUAC of 12.5 cm to reduce relapse rates. However, this would certainly increase the cost for treatment, as children would remain in SFPs longer (2).

Children with reported clinical signs of illness at the time of SFP admission were more likely to experience sustained recovery than those without illness. It may be possible that children who become malnourished because of an acute illness respond well to treatment and return to an improved overall nutrition status once the illness and associated acute malnutrition are reversed. Meanwhile, those without clinical signs of acute illness may be malnourished due to other longer-term underlying factors that leave the child susceptible to repeated episodes of acute malnutrition. For these children, the MUAC and weight gain during SFP treatment demonstrates recovery from the individual episode of acute malnutrition, but the underlying issues may continue to trigger further relapses.

With approximately half of all relapses occurring within the first three months of initial discharge from SFP, underlying physiological factors may not have fully recovered at the time of discharge, leaving the child susceptible to relapse. Previous studies have shown that immune function is often compromised during acute malnutrition (10, 15, 16) and may take longer to recover than MUAC or WHZ (17). However, in our sample we did not find abnormal serum complement C3 levels at the time of recovery, indicating normal function in at least this single immunological indicator. Serum complement C3 is one of many immune function indicators that can be explored. Further directed studies are warranted to identify the biological and sociological differences between children who sustain recovery and those that experience varying degrees of poor outcomes following MAM treatment. Given the global burden of MAM, generating such evidence is key to identifying the most effective treatment protocols to improve both the short- and long-term outcomes of children who recover from MAM.

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Tables and Figures

Table 1. Nutritional content of lipid nutrient supplement (LNS) provided as part of the intervention package to participants in the intervention group[1]

	LNS	IOM RDA[2] (1-3 years)
Total weight, g	40.0	
Energy, kcal	216.5	
Protein, g	5.3	13.0
Fat, g	15.2	
Minerals		
Biotin, mg	11.1	8.0
Calcium, mg	310.1	500.0*
Copper, mg	0.4	0.3
Iodine, µg	98.4	90.0
Iron, mg	8.2	1.3
Magnesium, mg	27.6	80.0
Manganese, mg	1.7	1.2*
Phosphorus, mg	541.1	460.0
Potassium, mg	368.2	3000.0*
Selenium, µg	24.4	20.0
Zinc, mg	3.5	0.9
Vitamins		
Folic acid, µg	213.0	150.0
Niacin, mg	8.2	6.0
Pantothenic acid, mg	2.7	2.0*
Riboflavin, mg	0.7	0.5
Thiamin, mg	0.6	0.5
Vitamin A, µg	452.1	300.0
Vitamin B-6, mg	0.6	0.5
Vitamin B-12, µg	1.2	0.9
Vitamin C, mg	36.0	15.0
Vitamin D, µg	11.9	5.0*
Vitamin E, mg	9.2	6.0
Vitamin K, µg	34.1	30.0*

[1]IOM, Institute of Medicine; LNS, lipid nutrient supplement; RDA, recommended dietary allowance.
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*Adequate Intake

Table 2.
Enrollment characteristics for intervention and control groups[1,2]

	Intervention (n = 769)	**Control** (n = 718)
Total clusters (clinic sites)	11	10
Female	472 (61)	435 (61)
Age, mo	17.01 ± 9.33	16.43 ± 9.08
Upon admission to initial treatment in SFP		
Type of treatment food received		
Received whey RUSF**	153 (20)	105 (15)
Received soy RUSF	155 (20)	128 (18)
Received RUTF**	460 (60)	485 (68)
MUAC, cm	12.10 ± 0.26	12.08 ± 0.27
WHZ	− 1.77 ± 0.66	− 1.76 ± 0.73
HAZ	− 2.73 ± 1.24	− 2.62 ± 1.37
Primary caretaker is mother	736 (97)	682 (97)
Mother alive*	756 (99)	696 (98)
Father alive	735 (97)	679 (96)
Mother known to be HIV+*	114 (18)	138 (22)
Fever in 2 weeks prior to admission	486 (67)	479 (71)
Diarrhea in 2 weeks prior to admission	468 (63)	459 (66)
Admission during harvest season (Apr-Aug)**	207 (27)	241 (34)
HFIAS score	8 ± 6	10 ± 6
Upon discharge from initial treatment in SFP		
MUAC, cm	12.78 ± 0.27	12.79 ± 0.27
MUAC gain, $mm \cdot d^{-1}$	0.29 ± 0.21	0.30 ± 0.21
WHZ	− 0.94 ± 0.73	− 0.88 ± 0.74
WHZ change	0.83 ± 0.51	0.88 ± 0.60
Weight gain, $g \cdot kg^{-1} \cdot d^{-1}$	2.77 ± 1.90	2.98 ± 2.37
Length gain, $mm \cdot d^{-1}$	0.30 ± 0.22	0.27 ± 0.22
Time to recovery, d	31.50 ± 20.60	31.92 ± 20.64
Child sleeps under bed net***	463 (60)	584 (81)
Child takes malaria prophylaxis	46 (6)	51 (7)
Child takes any supplements***	390 (51)	459 (64)
Child received deworming medication last month**	122 (17)	159 (24)

[1] Values are means ± SDs, n (%). HAZ, height-for-age z score; HFIAS, Household Food Insecurity Access Scale (0–27); HIV+, positive for human immunodeficiency virus; MUAC, mid-upper-arm circumference; RUTF, ready-to-use therapeutic food; RUSF, ready-to-use supplementary food; WAZ, weight-for-age z score; WHZ, weight-for-height z score.

[2] The intervention consisted of lipid nutrient supplement (LNS,) zinc supplementation, deworming, a bed net, and malaria chemoprophylaxis. *$P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 3. Comparison of primary outcomes between intervention and control groups from SFP discharge to 1, 3, 6, and 12 months follow-up between intervention and control groups[1-3]

	0 to 1 month			0 to 3 months			0 to 6 months			0 to 12 months		
	Interv (n = 769)	**Control** (n = 718)	*P*	**Interv** (n = 769)	**Control** (n = 718)	*P*	**Interv** (n = 769)	**Control** (n = 718)	*P*	**Interv** (n = 769)	**Control** (n = 718)	*P*
Sustained Recovery	604 (78)	531 (74)	0.038	530 (69)	455 (63)	0.024	491 (64)	421 (59)	0.039	407 (53)	347 (48)	0.076
Relapsed to MAM	153 (20)	161 (22)	0.233	209 (27)	215 (30)	0.238	230 (30)	234 (33)	0.265	281 (37)	260 (36)	0.895
Once	147 (19)	156 (22)	0.212	176 (23)	183 (25)	0.242	163 (21)	167 (23)	0.339	175 (23)	149 (21)	0.349
2 times	6 (1)	5 (1)	0.851	30 (4)	32 (4)	0.592	51 (7)	55 (8)	0.441	63 (8)	76 (11)	0.113
3 times	0 (0)	0 (0)	n/a	3 (0.4)	0 (0)	0.094	14 (2)	12 (2)	0.826	29 (4)	24 (18)	0.656
4 or more times	0 (0)	0 (0)	n/a	0 (0)	0 (0)	n/a	2 (0.3)	0 (0)	0.172	14 (2)	11 (2)	0.665
Developed SAM	6 (1)	13 (2)	0.077	14 (2)	21 (18)	0.161	18 (2)	24 (18)	0.244	27 (4)	46 (6)	0.010
Died	1 (0.1)	1 (0.1)	0.961	4 (0.5)	2 (0.3)	0.463	7 (1)	2 (0.3)	0.117	13 (2)	2 (0.3)	0.007
Death	0 (0)	1 (0.1)	0.301	2 (0.3)	2 (0.3)	0.945	4 (1)	2 (0.3)	0.463	7 (1)	2 (0.3)	0.117
Relapse then death	1 (0.1)	0 (0)	0.334	2 (0.3)	0 (0)	0.172	3 (0.4)	0 (0)	0.094	6 (1)	0 (0)	0.018
LTFU	5 (1)	12 (2)	0.064	12 (2)	25 (18)	0.018	23 (18)	37 (5)	0.034	41 (5)	63 (9)	0.009

[1] Values are *n* (%). Interv, intervention; LTFU, lost to follow-up; MAM, moderate acute malnutrition; SAM, severe acute malnutrition; SFP, supplementary feeding program.

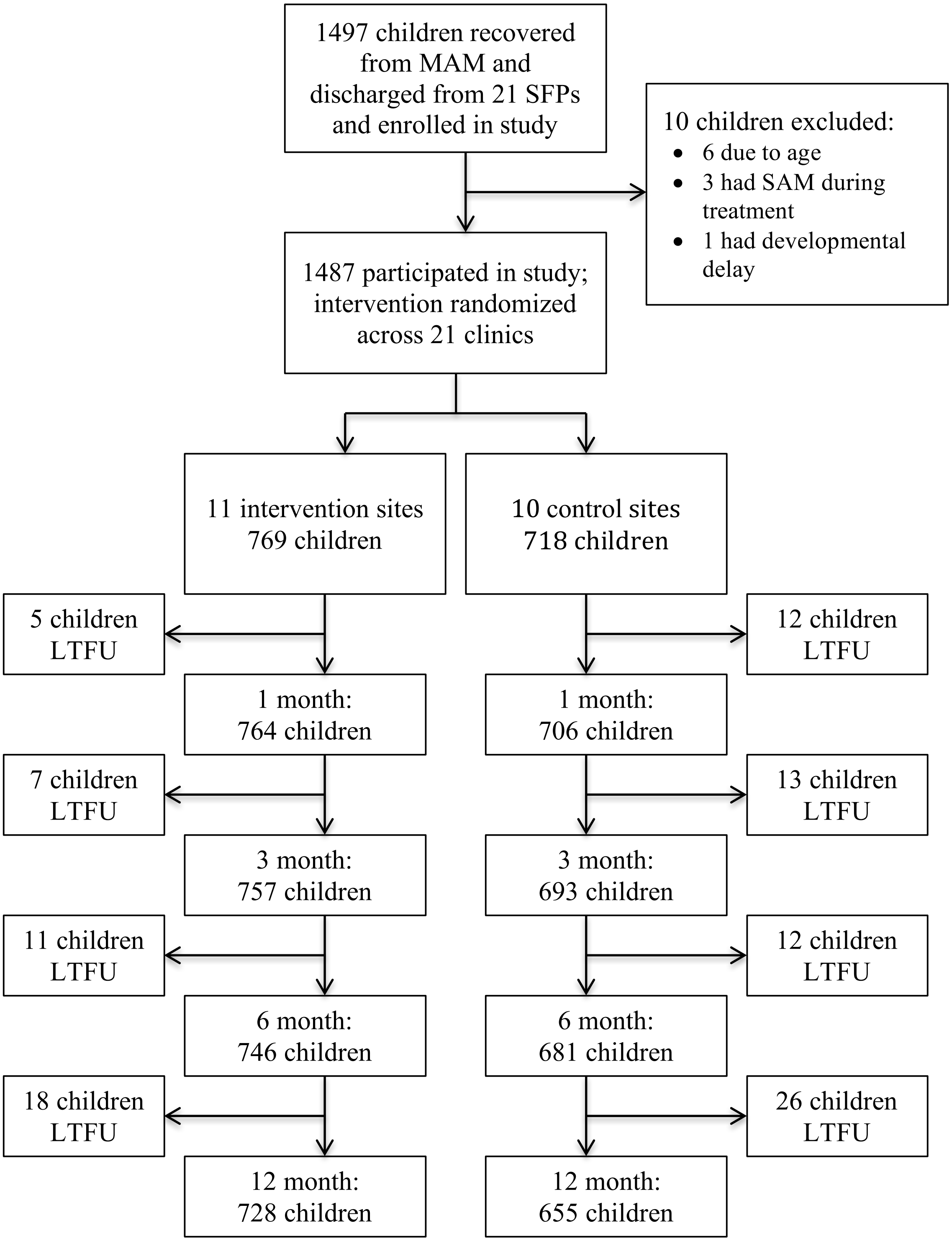
[2] The intervention consisted of lipid nutrient supplement (LNS,) zinc supplementation, deworming, a bed net, and malaria chemoprophylaxis.

Table 4.
Factors associated with children who sustained recovery for three, six, and twelve months following MAM treatment[1]

	Model for sustained recovery nourished for 3 months[3]		Model for sustained recovery nourished for 6 months[4]		Model for sustained recovery nourished for 12 months[5]	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Received intervention[2]	1.52 (1.22-1.90)	< 0.001	1.53 (1.17-2.00)	0.002	1.40 (1.06-1.85)	0.020
Age upon SFP admission, m	1.12 (1.01-1.03)	0.002	1.03 (1.02-1.04)	< 0.001	1.02 (1.01-1.03)	0.004
MUAC upon SFP admission, mm	1.17 (1.12-1.21)	< 0.001	1.15 (1.12-1.20)	< 0.001	1.19 (1.15-1.24)	< 0.001
WHZ upon SFP admission	0.47 (0.37-0.60)	< 0.001	0.57 (0.45-0.73)	< 0.001	0.51 (0.37-0.72)	< 0.001
Fever in 2 weeks prior to SFP admission	1.42 (1.04-1.93)	0.026	*not significant*		1.31 (1.05-1.62)	0.018
Diarrhea in 2 weeks prior to SFP admission	*not significant*		1.52 (1.12-2.05)	0.007	*not significant*	
HFIAS score upon SFP admission	1.03 (1.02-1.04)	< 0.001	1.02 (1.00-1.04)	0.023	1.02 (1.01-1.03)	0.006
MUAC upon SFP discharge, mm	1.14 (1.06-1.23)	0.001	1.10 (1.05-1.15)	< 0.001	*not significant*	
MUAC change during SFP treatment, $mm \cdot d^{-1}$	*not significant*		3.11 (1.47-6.56)	0.003	5.80 (3.05-11.03)	< 0.001
WHZ upon SFP discharge	2.61 (1.97-3.48)	< 0.001	2.35 (1.72-3.22)	< 0.001	2.70 (1.87-3.91)	< 0.001
Mother known to be HIV+	1.38 (1.07-1.79)	0.013	*not significant*		1.26 (1.03-1.54)	0.029
Child previously slept under bed net	1.35 (1.03-1.77)	0.028	1.33 (1.06-1.68)	0.013	1.38 (1.10-1.73)	0.006

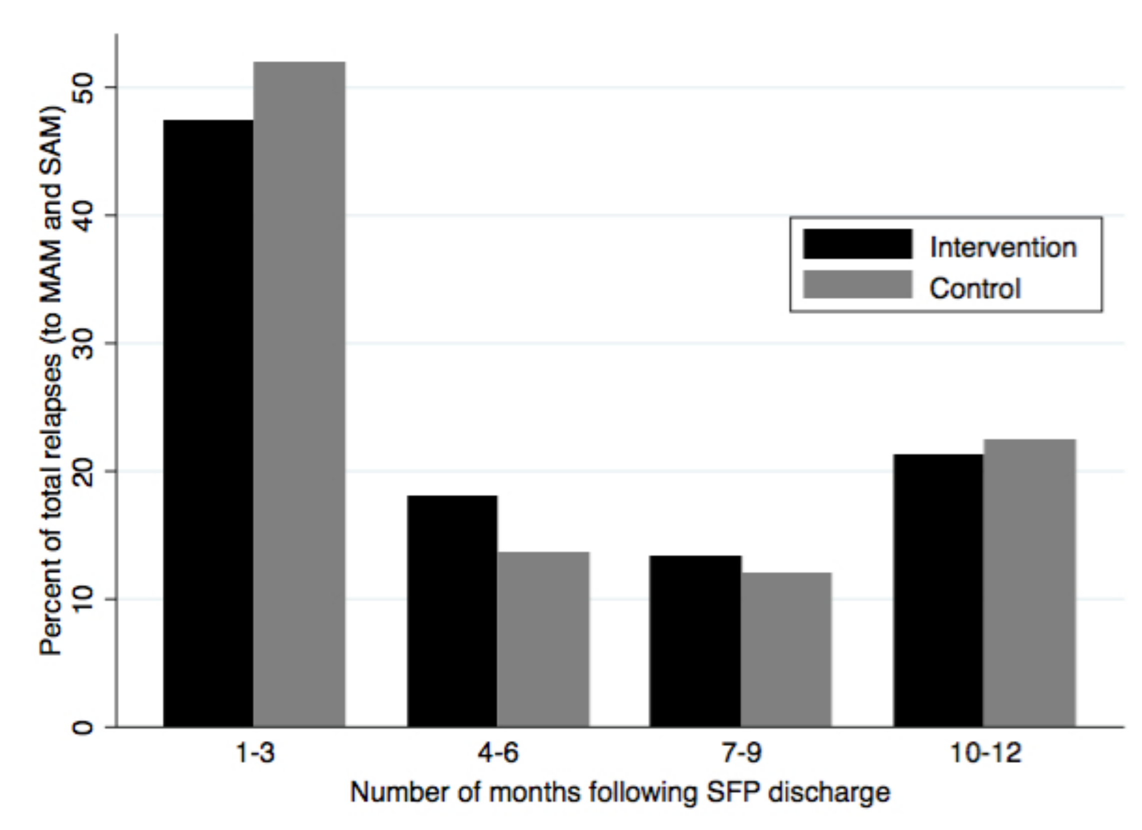
[1] Binary logistic regression models constructed with robust standard errors to account for clustering and using a backward elimination method, retaining only those factors with P < 0.05. CI, Confidence Interval; MUAC, mid-upper-arm circumference; HFIAS, Household Food Insecurity Access Score (0-27); WHZ, weight-for-height Z-score; HIV, Human Immunodeficiency Virus
[2] The intervention consisted of lipid nutrient supplement (LNS,) zinc supplementation, deworming, a bed net, and malaria chemoprophylaxis.
[3] Logistic regression; Model Pseudo R^2 = 0.094; R^2 = 0.113 by Cox and Snell
[4] Logistic regression; Model Pseudo R^2 = 0.098; R^2 = 0.123 by Cox and Snell
[5] Logistic regression; Model Pseudo R^2 = 0.085; R^2 = 0.111 by Cox and Snell; Likelihood ratio test and Wald test confirm the final model has stronger predictive power without the variable “MUAC upon Discharge from SFP”

Figure 1.
Flow of participants through the cluster randomized controlled clinical trial[1]



[1] MAM, moderate acute malnutrition; LTFU, loss to follow-up; SAM, severe acute malnutrition; SFP, supplementary feeding program.

Figure 2. Percent of total relapses to MAM and developments of SAM for control and intervention groups by number of months from initial SFP discharge[1]



[1] MAM, moderate acute malnutrition; SAM, severe acute malnutrition; SFP, supplementary feeding program.

Supplemental Table 1. Characteristics of those who sustained recovery vs. those who did not.

	Sustained Recovery (n = 754)	**Did not sustain recovery** (n = 733)	*P*
Female	460 (61)	447 (61)	0.991
Age, mo	17.72 ± 9.78	15.72 ± 8.48	0.050
Upon Admission to Initial Treatment in SFP			
Type of treatment food received			
Received Whey RUSF	120 (16)	138 (19)	0.135
Received Soy RUSF	129 (17)	154 (21)	0.054
Received RUTF	505 (67)	440 (60)	0.006
MUAC, cm	12.12 ± 0.26	12.05 ± 0.27	0.018
Weight, kg	7.44 ± 1.28	7.16 ± 1.14	0.034
Length, cm	72.11 ± 7.35	70.60 ± 6.74	0.034
WHZ	− 1.77 ± 0.70	− 1.77 ± 0.68	0.954
HAZ	− 2.69 ± 1.33	− 2.67 ± 1.28	0.832
WAZ	− 2.77 ± 0.82	− 2.77 ± 0.77	0.992
Primary caretaker is mother	727 (98)	691 (96)	0.176
Mother alive	736 (98)	716 (99)	0.557
Father alive	718 (97)	696 (96)	0.602
Mother known to be HIV+	142 (22)	110 (18)	0.052
Fever in 2 weeks prior to admission	513 (72)	452 (66)	0.027
Diarrhea in 2 weeks prior to admission	490 (67)	437 (61)	0.025
Admission during harvest (Apr-Aug)	236 (31)	212 (29)	0.318
HFIAS score	9.22 ± 5.96	8.75 ± 5.92	0.695
Food secure	78 (11)	81 (11)	0.656
Mild food insecurity	25 (24)	25 (4)	0.921
Moderate food insecurity	123 (17)	98 (14)	0.111
Severe food insecurity	508 (69)	509 (71)	0.365
Upon Discharge from Initial Treatment from SFP			
MUAC, cm	12.83 ± 0.30	12.73 ± 0.23	0.002
MUAC gain, $mm \cdot d^{-1}$	0.33 ± 0.23	0.26 ± 0.18	0.008
WHZ	− 0.88 ± 0.73	− 0.95 ± 0.74	0.472
WHZ change	0.89 ± 0.56	0.83 ± 0.55	0.237
Weight gain, $g \cdot kg^{-1} \cdot d^{-1}$	3.26 ± 2.32	2.46 ± 1.85	0.015
Length gain, $mm \cdot d^{-1}$	0.27 ± 0.23	0.29 ± 0.21	0.272
Time to recovery, d	29.04 ± 19.29	34.45 ± 21.56	0.017
Child sleeps under bed net	541 (72)	506 (69)	0.250
Child takes malaria prophylaxis	55 (7)	42 (6)	0.217
Child takes any supplements	461 (61)	388 (53)	0.002
Child received deworming medication last month	154 (22)	127 (81)	0.116

[1]Values are means ± SDs, n (%). HAZ, height-for-age z score; HFIAS, Household Food Insecurity Access Scale (0–27); HIV+, positive for human immunodeficiency virus; MUAC, mid-upper arm circumference; RUTF, ready-to-use therapeutic food; RUSF, ready-to-use supplementary food; WAZ, weight-for-age z score; WHZ, weight-for-height z score.

Addendum 1. Additional results not included in the published article that comprises Chapter 2

Primary outcomes regarding the proportion of children who relapsed to MAM, SAM, and who were lost to follow-up (LTFU).

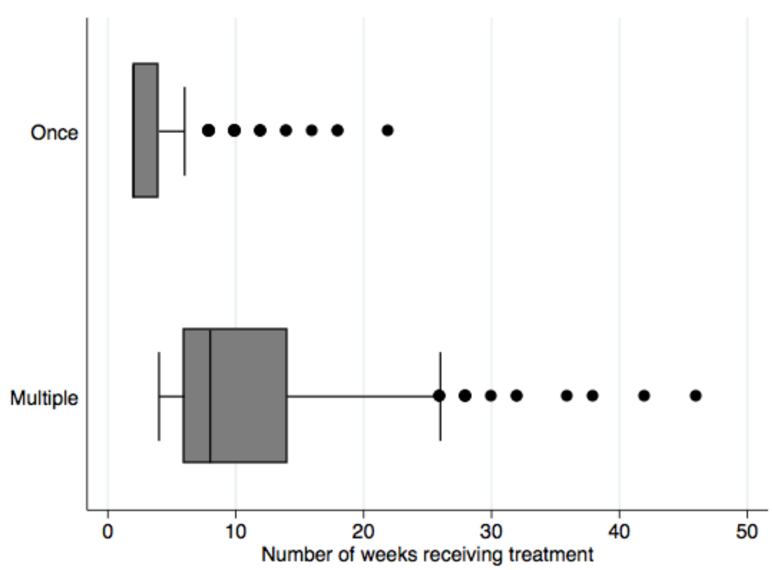
No significant difference was observed in the proportion of children who relapsed to MAM (either once or multiple times) in the control vs. intervention groups. The proportion of children who developed SAM and those who died were also similar across groups, with the exception of the intervention group experiencing slightly more of each outcome at the 12-month visit (6% vs. 4% developed SAM for intervention and control groups, respectively, $P = 0.01$; 2.0% vs. 0.3% died for intervention and control groups, respectively, $P < 0.007$).

The number of LTFU was greater in the control group at all follow-up visits, including 12 (2%) vs. 5 (1%) ($P < 0.1$) at one month, 25 (3%) vs. 12 (2%) ($P < 0.05$) at three months, 37 (5%) vs. 23 (3%) ($P < 0.05$) at six months, and 63 (9%) vs. 41 (5%) ($P < 0.01$) at 12 months, for the control and intervention groups, respectively (Table 3 in Chapter 2). Half of those who were LTFU moved; 25% lived in Mozambique; and 25% were LTFU for unknown reasons. Several SFP clinics were located near the Mozambican border and served many Mozambicans; subsequently, several were enrolled into the study. Mozambique is an area where Malawian CHWs are not permitted to travel, which limited their ability to reach caregivers at their homes and remind them to return to the next follow-up visits. The second largest clinic site was a control site and located near the Mozambican border, which accounted for almost 30% of all the LTFU in the study. A comparison of baseline characteristics between children who were LTFU and those that completed the study revealed no major differences between the two types of participants. Results showed those who were LTFU had fewer mothers as the primary caregivers and fewer children took supplements. Given the different proportions of LTFU between control and intervention sites, primary outcomes were also analyzed without those who were LTFU. The statistical significance regarding the impact of the intervention on the proportion of children who sustained recovery is similar when analyzing the data with and without those who were LTFU.

Additional figures comparing nutritional trajectories of children who relapsed to MAM once versus those who relapsed to MAM multiple times

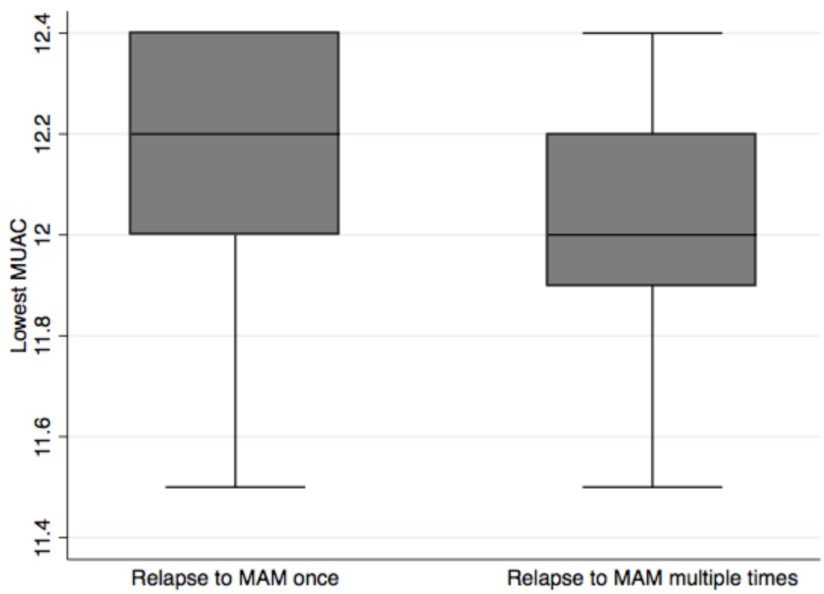
Those who relapsed to MAM multiple times required longer treatment for those relapses during the follow-up period than those who relapsed only once ($P < 0.001$) (**Figure 1**). MUAC dropped significantly lower among those who relapsed to MAM multiple times compared to those who relapsed only once ($P < 0.001$) (**Figure 2**).

Figure 1. Number of weeks receiving treatment for those who relapsed to MAM once vs. those who relapsed to MAM multiple times[1]



[1]Mean (SD) number of weeks was 3.63 ± 2.92 for those who relapsed once and 11.12 ± 7.63 for those who relapsed multiple times ($P = 0.001$). MAM, moderate acute malnutrition.

Figure 2. Lowest MUAC during the follow-up period for those who relapsed to MAM once vs. those who relapsed to MAM multiple times[1]



[1]Mean (SD) lowest MUAC was 12.18 ± 0.22 for those who relapsed once vs. 12.03 ± 0.23 for those who relapsed multiple times ($P < 0.001$). MAM, moderate acute malnutrition; MUAC, mid-upper arm circumference.

Linear growth following recovery from MAM

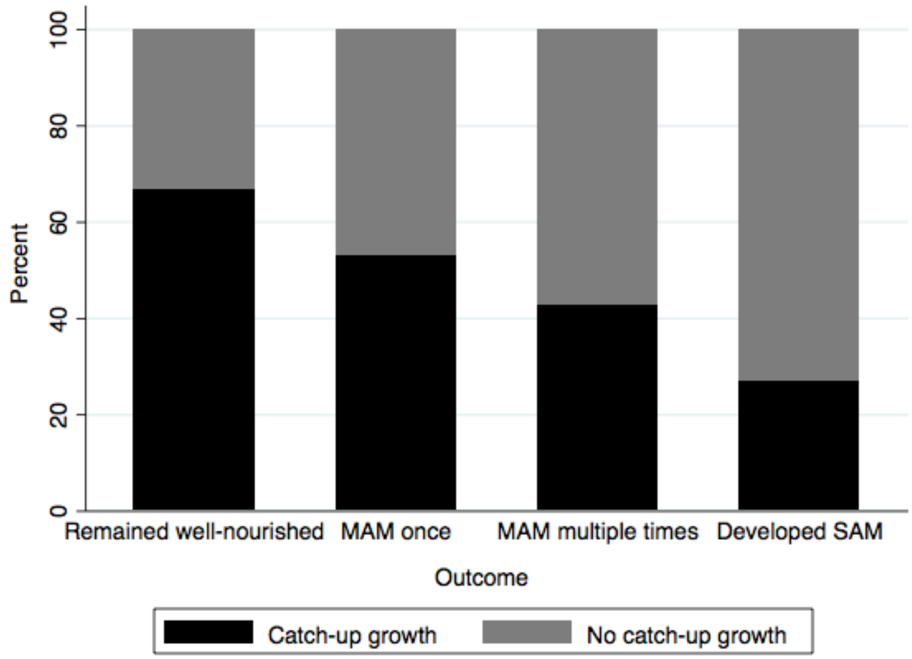
Across both groups, only 55% of children experienced a positive change in HAZ score from the time of SFP discharge to the end of the 12-month follow-up period. The proportion of children who experienced this positive linear growth was highest among those who sustained recovery (63%), followed by 45% of those that relapsed to MAM once, 38% of those who relapsed to MAM multiple times, and 25% of those who developed SAM, irrespective of whether they received the intervention (**Figure 3**). This trend of poor linear growth rates among those who experience multiple and more severe relapses is also seen when comparing average change in HAZ score across outcomes:

+0.15, -0.03, -0.17, and -0.53 HAZ change for those who sustained recovery, relapsed to MAM once, relapsed to MAM multiple times, and developed SAM respectively. Differences in HAZ change were all statistically significant at least $P < 0.05$ (**Figure 4**).

Our results revealed a strong relationship between poor linear growth and relapse to acute malnutrition following the recovery from MAM. This association is seen across all outcomes, with the worst linear growth rates being associated with multiple and more severe relapses, while the best linear growth rate is associated with sustained recovery. These findings contribute to a growing body of evidence that more closely links poor linear growth with acute malnutrition (15, 16). The high rate of poor growth following MAM seen in our study corroborates other research that suggests acute malnutrition may have a direct impact on the trajectory of linear growth (15).

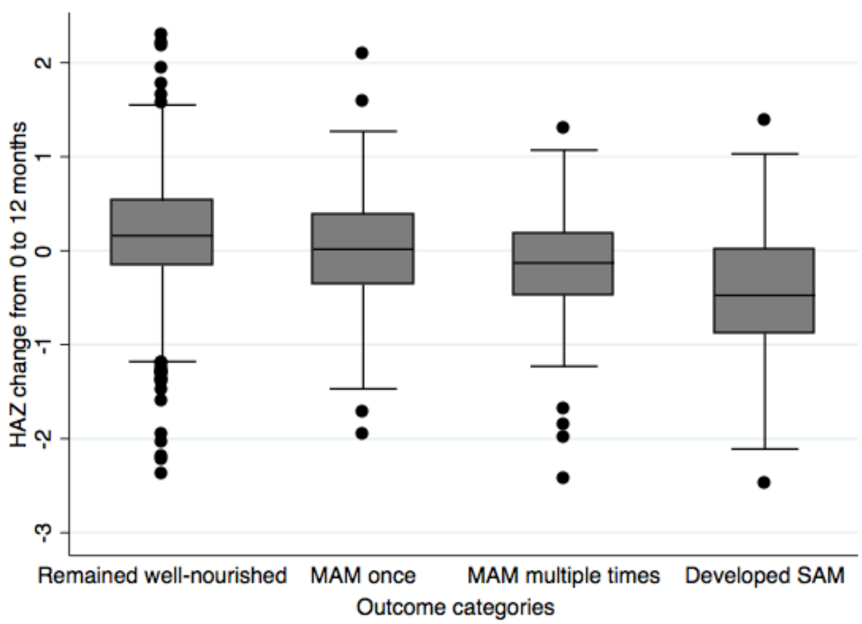
Interestingly, neither low HAZ nor poor linear growth rate during SFP treatment was predictive of relapse after recovery. Although it is worth noting that time spent in a supplementary feeding program can be quite short (frequently as few as four weeks), which may be such a brief period of time that linear growth rate is not well captured.

FIGURE 3. Percent of children who experienced catch-up growth (defined as positive HAZ change) during the year following discharge from SFP by outcome[1]



[1] MAM, moderate acute malnutrition; SAM, severe acute malnutrition; SFP, supplementary feeding

FIGURE 4. Change in HAZ from 0 to 12 months following initial recovery from MAM[1]



[1] HAZ, height for age z score; MAM, moderate acute malnutrition; SAM, severe acute malnutrition. Statistically significant differences in mean HAZ change between remained well nourished and relapsed to MAM once at $P < 0.01$; relapsed to MAM once vs. relapsed to MAM multiple times at $P < 0.05$; relapsed to MAM multiple times vs. developed SAM at $P < 0.01$.

Chapter 3. Household-level factors associated with relapse following initial recovery from moderate acute malnutrition

Abstract

Background: Factors associated with relapse among children who successfully recover from moderate acute malnutrition (MAM) are not well understood.

Objective: The aim of this study was to identify household (HH) level factors associated with whether or not a child sustains recovery, defined as maintaining a mid-upper arm circumference (MUAC) ≥ 12.5 cm, for one year following recovery from MAM.

Design: We conducted a study analyzing data from an in-depth HH survey on a sub-sample of participants within a larger cluster randomized controlled trial that followed children for one year following recovery from MAM after treatment in a supplementary feeding program. Data collected from the HH survey consisted of indicators pertaining to: 1) socioeconomic status (SES), 2) infant and young child feeding (IYCF) practices, 3) household food security, 4) water, sanitation, and hygiene (WASH), and 5) maternal perceptions of MAM, the supplementary feeding program (SFP), and relapse following MAM recovery. The HH survey was administered at the time of discharge from MAM treatment in an SFP. Children were then followed for one year to collect outcome data regarding whether or not recovery was sustained.

Results: Out of the 1497 children participating in the larger cluster randomized controlled trial, a total of 315 participated in this sub-study. Significant predictors of sustained recovery included MUAC at the time of SFP discharge ($P < 0.001$) and HHs that had fitted lids on all water storage containers ($P < 0.01$). Also, caregivers with clean hands

($P < 0.1$) and use of an improved sanitation facility ($P < 0.1$) were marginally significant predictors of HHs having a child that sustained recovery. Socioeconomic status, food security, and IYCF practices were not statistically different between HHs with children who sustained recovery and HHs with children that did not.

Conclusion: Our study shows that very few HH level indicators are predictive of whether a child sustains recovery. Although results hint that improved WASH conditions may help to reduce the proportion of children who relapse following recovery from MAM, larger clinical trails would be need to confirm this. MUAC at the time of SFP discharge is strongly associated with sustained recovery, suggesting that increasing the MUAC discharge criterion may improve relapse rates during one year following initial MAM recovery.

Introduction

Relapse has been shown to be common in the few studies that have followed children after initial recovery from moderate acute malnutrition (MAM) (1, 2). Previous research by our team in Malawi found only 51% - 63% of children sustain recovery for 12 months following initial treatment for MAM (1). Common childhood illnesses, such as fever, cough, malaria, and diarrhea, have been shown to be prevalent among those who relapse or die after initial MAM recovery (1, 3-5). Poor linear growth has also been observed in children following treatment for MAM and severe acute malnutrition (SAM) (6). A Malawian study found mid-upper arm circumference (MUAC) and weight-for-height z-score (WHZ) at enrollment and discharge from a supplementary feeding program (SFP) have shown to be predictive of relapse during the following year, while length of treatment was not (7). A recent study from Burkina Faso of a mixed population of children (90% MAM and 10% SAM) reported associated factors to relapse included low MUAC at discharge, low oil/fat consumption during the follow-up period, and incomplete vaccination (8). Regarding children being treated for severe acute malnutrition (SAM), a study in Kenya identified children with HIV to have higher risk of relapse following treatment for SAM, than those without HIV (9). These studies begin to shed light on factors associated with relapse, yet large gaps in knowledge still remain.

It is plausible that returning to an unchanged household environment (that may very well have contributed to the development of MAM in the first place) following recovery from MAM may play a role in causing children to relapse. Infant and young child feeding practices (10-13), unsanitary living conditions (14, 15), poor food security and dietary diversity (16, 17), and socioeconomic status (18, 19) have all been linked to acute malnutrition; still, no prior studies have directly measured these factors with relapse following initial recovery from acute malnutrition. Identifying household risk factors associated with relapse could have significant implications on how best to prevent relapse and improve the sustainability of MAM treatment. In order to identify such factors, we conducted a study analyzing data from an in-depth household survey on children who were followed for one year after recovery from MAM.

Subjects and Methods

Study Design

This study consisted of an in-depth household (HH) survey administered prospectively, at the time of SFP discharge, to a randomly selected sub-sample of participants within a larger cluster randomized controlled trial (cRCT) examining relapse following MAM recovery. Complete methods of the larger cRCT have previously been described in detail (See Chapter 2)[5]. In brief, children aged 6-62 months who had recovered from MAM, defined as MUAC ≥ 12.5 cm without bipedal edema (20), were recruited from rural health clinics in southern Malawi. Eleven of the health clinics were randomly allocated to receive nutrition counseling plus a package of health and nutrition interventions at the time of SFP discharge, while 10 health clinics were randomly selected to receive nutrition counseling only. Children were followed for 12 months following SFP discharge to assess the impact of the package of health and nutrition services on increasing the proportion of children that sustained recovery for one year following treatment for MAM. The study was conducted in rural Malawi where most of the population consists of poor, subsistence farmers. Living conditions are often unsanitary, without access to clean drinking water, and household are often at far distances from functioning health clinics. Child malnutrition is widespread with over 40% of children under 5 years old being stunted and 17% underweight (21).

The aim of this study was to identify various HH factors relating to socioeconomic status, dietary diversity, food insecurity, child care practices, and water, sanitation and hygiene that may be associated with whether or not a child sustained recovery following discharge from an SFP. Sustained recovery was defined as maintaining MUAC ≥ 12.5 cm without bipedal edema for one year following initial treatment for MAM. The HH survey was only conducted among children who did not receive an intervention.

[5] The content in Chapter 2 of this dissertation contains details of the full cluster randomized controlled trial.

Subject Participation

Children were enrolled in the study at the time of recovery from MAM and subsequent discharge from an SFP. Informed consent was obtained from all caregivers. Upon enrollment, participants in the study scheduled an appointment for a data collector to travel to the caregiver's home within one week of the child's discharge from SFP. A trained data collector, either a senior pediatric research nurse or a community health worker, administered the survey at the home of the caregiver. Information collected consisted of socio-demographic characteristics, child dietary diversity, infant and young child feeding practices, and water hygiene and sanitation factors that have been shown to be associated with child health and nutrition outcomes. Caregivers were also asked about their perceptions on the SFP, MAM, and relapse. The survey lasted approximately one hour.

Caregivers were asked to return to the clinic for subsequent follow-up visits at 1, 3, 6, and 12 months after enrollment to reassess the child's nutrition status and clinical signs of illness, including diarrhea and fever. Household food security was also assessed at each follow-up visit using the validated, nine-item Household Food Insecurity Access Scale (HFIAS) (22).

At the end of the 12 month follow-up period, each child was classified as having "sustained recovery", defined as having MUAC $\geq$ 12.5 cm at every follow-up visit for 12 months; "relapsed to MAM", defined as MUAC $<$ 12.5 cm and $\geq$ 11.5 cm at any point during the follow-up period; "developed SAM", defined as MUAC $<$ 11.5 cm and/or bipedal edema (kwashiorkor) at any point during the follow-up period; "died"; or "lost to follow-up," defined as defaulting on a scheduled visit and never returning. Poor outcomes were considered to be relapsing to MAM, developing SAM, lost to follow-up, or death. If a child experienced two such outcomes over the course of the follow-up period, the more severe category was assigned as the final outcome.

Ethical Approval

The study was approved by the University of Malawi's College of Medicine Research and Ethics Committee, Washington University's Human Research Protection Office, and Tufts University's Internal Review Board. Permission to conduct the study was obtained by each site's District Health Officer and/or District Nutritionist.

Household Survey

Data collected from the HH survey consisted of information pertaining to: 1) socioeconomic status (SES), 2) infant and young child feeding (IYCF) practices, 3) household food security, 4) water, sanitation, and hygiene (WASH), and 5) maternal perceptions of MAM and relapse following MAM.

SES. In order to measure SES, we collected indicators based on a recently validated SES index by Psaki et al. (23) in an eight-country study. This index, called the WAMI index, was comprised of four main components—water and sanitation, assets, maternal education, and household income. WAMI was chosen due to its simplified nature and associations with child HAZ (23). However, in this study, monthly household income was not collected (as it is in the WAMI) due to many of the families in this context having informal avenues of income and fluctuating monthly income (19). To account for this deviation, we collected information on additional assets and livestock to help distinguish different levels of wealth within the local context. We conducted principal component analysis (PCA) (24)—a technique that creates a single variable (the index) through the summation of individual weighted variables—on various combinations of indicators relating to maternal education, household characteristics, and asset ownership. However, individual indicators were not correlated enough, as indicated by low Cronbach's alphas below 0.65 and low factor loadings in a PCA analysis, to generate one overall SES index.

We estimate the low correlations among indicators may be due to the population being extremely homogeneous, as many of the indicators lacked variability. For example, 97% of caregivers' highest level of education is primary school only (less than a 8 years of schooling). As shown by Psaki et al. in (23), education level often correlates with wealth. However, in this study, there is no correlation between number of HH assets owned and education completed by caregivers, with the exception of the very few (<3%) who completed education beyond primary school. Therefore, rather than using one overall SES index, the following individual variables were included in the final regression model: maternal education, number of rooms in a house, ownership of any livestock, and number of household assets (out of 11 total). **Table 1** contains information on the definition and scoring of each indicator relating to SES.

IYCF Practices. Indicators included in the HH survey regarding IYCF practices were based on current international recommendations for infant and young child feeding practices (25, 26). Indicators included: 1) breastfeeding practices; 2) the introduction of complementary foods, 3) minimum meal frequency, and 4) minimum dietary diversity. Because recommended feeding practices vary according to age (12, 25, 26), information used in the breastfeeding practices and minimum meal frequency indicators differed according to the age of the child. This ensured that the indicators were age appropriate.

Table 2 contains information on the definition and scoring of each indicator regarding IYCF practices.

Food Security. Household food security was assessed using HFIAS (22), which contains a series of nine questions regarding the food security situation at the household level. Scores range from 0 to 27 with higher scores representing increased food insecurity while lower scores represent better food security. This was administered to the caregiver at the time of admission into SFP as well as one, three, six, and twelve months following SFP discharge. Scores from all time points throughout the year were averaged. Food security can and often does change throughout the year between times when food availability is higher, during post harvest, and times when food is scarcer prior to harvest. (Changes in participants' HFIAS scores between visits ranged from 0 to 23 and averaged a 10-point difference between the lowest and highest HFIAS scores across follow-up visits.) An average over the course of the year was chosen to help account for these changes throughout the year.

WASH. WASH Indicators used in program evaluations by international agencies (27-29) as well as the 2011 Demographic and Health Survey (DHS) (30) were used to capture WASH conditions and practices among participating households. Given prior associations between cleanliness of hands and child health outcomes (31, 32), the caregiver's hands and the child's hands were visually inspected for cleanliness, which included a three-point scale denoting "clean," "no visible dirt but unclean appearance," and "visible dirt" regarding the palms, finger pads, and finger nails (27). During data collection training, data collectors underwent several examples of proper scoring, including tests of intra- and inter-rater reliability. This included large group demonstrations and small group exercises (where groups of four to five enumerators practiced scoring each other's hands and testing how consistent scores were). A final test was administered at the end of the training to ensure proper scoring was understood. Use of improved water sources and sanitation facilities was based on the WHO definitions (29, 30). Respondents were asked if they take action to treat water, following DHS format (30). Water storage containers were assessed for having fitted lids (33). Hygiene was assessed by direct observation of whether or not a caregiver used soap during a hand washing demonstration (27, 28), knowledge regarding five critical times for hand washing (28, 30, 33), and the frequency in which the child is bathed (34). **Table 3** contains information on the definition and scoring of each WASH indicator.

Statistical Analyses

All data were double entered into an Access (Microsoft Corp., Redmond WA) database and verified against original forms when discrepancies were identified. Bivariate analyses was conducted using student's t test for continuous variables and chi-squared for binary variables with adjustment for clustering at the health clinic level in order to compare individual indicators between HHs with children who sustained recovery for 12 month following discharge from SFP and those that did not. P-values < 0.05 were considered to be statistically significant. All statistical analysis was conducted using Stata Version 13.0 (StataCorp LP, College Station, TX).

Binary logistic regression was used to identify which indicators were associated with sustained recovery while accounting for other factors. Cluster-adjusted robust standard errors were used to account for the clustering at the health clinic level. Variables used in the full model included sex, age at the time of admission to SFP, whether the child had fever during the 2 weeks prior to admission into the SFP, whether the child had diarrhea during the 2 weeks prior to admission into the SFP, discharge MUAC, discharge WHZ score, years of education completed by the caregiver, number of rooms in the house, whether any livestock was owned, number of HH assets owned (out of 11), whether the child was currently breastfeeding at the time of SFP discharge (for children under 24 months) or whether the child continued to breastfeed up to age 24 months (for children over 24 months), minimum dietary diversity, minimum meal frequency, average HFAIS score from all follow-up visits, if all drinking water was retrieved from improved water source, use of an improved sanitation facility, cleanliness of caregiver's hands, cleanliness of child's hands, and whether the child was bathed daily during the previous week.

Results

Out of the 1487 children analyzed in the larger cRCT, a total of 315 were enrolled in this study that completed the in-depth HH survey. Three surveys were excluded due to uninterpretable data, leaving a total of 312 for final analysis. The proportion of children who sustained recovery for the duration of the 12-month follow-up period after initial recovery from MAM was 58% (**Table 4**).

In bivariate analysis comparing household indicators between those who sustained recovery and those that did not, few individual indicators differed. A larger proportion (44%) of HHs with a child who sustained recovery had lids on all water storage containers (as opposed to some or all storage containers *without* lids) than those HHs whose child did not sustain recovery (32%) ($P < 0.05$) (**Table 4**). Although not statistically significant, caregivers' hands were observed to be cleaner among children who sustained recovery ($P = 0.142$). Also, the proportions of HHs that used an improved sanitation facility or improved sources for drinking water were nearly double among the sustained recovery group ($P = 0.077$ and $P = 0.225$ for improved sanitation facility and sources of drinking water, respectively). No differences were found between the two groups regarding SES indicators, IYCF practices, food security, or maternal perceptions of SFP, MAM, and relapse.

Similar results were found when controlling for other factors in binary logistic regression (**Table 5**). HHs that had fitted lids on all water storage containers were more likely to have a child that sustained recovery than those who did not have lids on all storage containers (OR=1.79, 95% CI: 1.20-2.68, $P < 0.01$). Although only marginally statistically significant, apparent cleanliness of caregivers' hands (OR=2.47, 95% CI: 0.99-6.18, $P < 0.1$) and HH use of an improved sanitation facility (OR=1.46, 95% CI: 0.95-2.26, $P < 0.1$) were associated with having a child sustain recovery. HH socioeconomic status, food security, and IYCF practices were not statistically different between the two groups. On an individual level, children with a higher MUAC upon discharge from initial MAM treatment in an SFP were more likely to sustain recovery than those with a lower discharge MUAC (OR=1.20, 95% CI: 1.09-1.31, $P < 0.001$).

Discussion

Our results show that improved WASH factors, including caregivers having clean hands, HHs having fitted lids on water storage containers, and HHs using an improved sanitation facility, were associated with a child sustaining recovery for 12 months after treatment for MAM. Interestingly, factors related to SES, food security, or IYCF practices were not at all associated with sustained recovery. These results suggest that interventions to improve WASH conditions may help to reduce the proportion of children who relapse following recovery from MAM.

Although many studies have been conducted regarding the impact of WASH on child health outcomes, such as diarrhea (35) and helminthes infection (36), fewer and less rigorous studies have been employed regarding nutritional outcomes and show little evidence of impact. A recent Cochrane review identified five cluster randomized controlled trials that measured the effect of WASH interventions on nutritional status and found no evidence that WASH interventions have an impact on weight-for-age z score (WAZ) or WHZ, and only a small effect on height-for-age z score (37) (38). Still, the interventions were short in duration; no study considered the effect of a complete package of WASH interventions; and no study examined the impact on relapse rates following initial recovery from MAM. A prospective, randomized trial that examines the impact of a package of WASH interventions on relapse among children following recovery from MAM is warranted.

Furthermore, studies are needed to generate a better understanding of the potential causal pathways between WASH conditions and sustained recovery from MAM. This includes in-depth biological analyses regarding diarrheal diseases, intestinal parasite infections and environmental enteric dysfunction (EED) during and following the state of moderate malnutrition. Diarrhea and intestinal parasites have well been shown to exacerbate acute malnutrition (39-42), and if gone untreated at the time of discharge from SFP could leave children susceptible to relapse. Results from the larger cRCT, in which this current study was embedded, found that providing a single dose of deworming medication and a 14-day course of zinc supplementation at the time of SFP discharge (as part of a larger package of services) had a marginal, but statistically significant impact on improving the proportion of children that sustained recovery following MAM treatment (See Chapter 2). Also, another recent study shows frequent subclinical inflammation in children with MAM (43), a likely sign of EED. In theory, if EED is present in children with MAM, it may play a role in the poor linear growth observed in children who relapse following recovery from MAM (see Chapter 2), given that many experts hypothesize that EED hinders linear growth (44-46). Still, further research is needed to measure EED directly in moderately malnourished children in order to conclude if a relationship exists between WASH, EED, and relapse.

While evidence from this study points to the potential for improved HH WASH conditions to reduce relapse rates following recovery from MAM, this is likely one of many factors that must be explored in order to improve MAM treatment such that recovery is better sustained. For example, our study demonstrates that a higher MUAC at SFP discharge is predictive of sustaining recovery during the following year. Improved WHZ and MUAC at the time of admission and discharge from MAM treatment have also been observed in other studies (1, 7). For example, in an observational study in Malawi, Trehan et al. (7) found that higher WHZ at discharge was more predictive of sustained recovery than longer duration of treatment. Therefore, increasing the MUAC cut-off for SFP discharge may have a significant impact on reducing relapse rates following SFP.

With the exception of a few WASH indicators, our results show the vast majority of HH characteristics and caregiving practices in this context did not greatly differ between HHs whose children who relapsed and those who sustained recovery. In this very homogeneous and low-income population, factors relating to SES, IYCF practices, and food security that have previously proven to be associated with child malnutrition and health outcomes (10-13, 16-19) do not distinguish between those who sustain MAM recovery and those who do not. This may suggest that relapse is less a result of household conditions and more associated with the individual child's health and nutrition status. Certainly household conditions are important to the overall well being of children, and improvement in such circumstances should remain the goals in public health interventions and development programs. Yet increasing nutrition sensitive programming alone is not likely to dramatically reduce the large percent of children experiencing relapse following MAM. Rather, these programs should be considered an important complement to improved SFP treatment and follow-up protocols that address risk factors or relapse at the level of the individual child.

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Tables and Figures

Table 1.
SES indicators from the HH survey[1]

Indicator	Definition	Range
Maternal education	Number of years of completed education, ranging from no education up to "Form 4", the completion of primary and secondary education in Malawi. This equals 12 years of education. No respondents completed any higher education beyond Form 4.	0-12
Ownership of assets	Assets owned by anyone in the home. These include a mattress, bicycle, chair or bench, radio, mobile phone, flashlight, cabinet, pair of shoes, candle, lantern, and bank account.	0-11
Number of rooms in house	Number of separate rooms in a house. The term “separate” was defined as a physical wall, which did not include sheets or curtains dividing a space. The minimum and maximum number of rooms reported was 1 and 6, respectively.	1-6
Ownership of livestock	If anyone in the home owned any livestock. These include chickens, goats, cattle, dogs, pigs, or guinea fowl. This was considered an asset rather than a separate livelihood given the fact that all participants are agriculturists and the ownership of animals would be an additional indication of wealth.	0, 1

[1] HH, household

Table 2.
IYCF indicators from the HH survey[1]

Indicator	Definition	Range
Continued Breastfeeding	Continued breastfeeding until at least 24 months is recommended (25, 26). Therefore, in this indicator if the child was below 24 months or younger, they received a score of 1 if they were currently breastfeeding and 0 if they were not. For children over 24 months, they received a 1 if the age in which they stopped breastfeeding was beyond 24 months and 0 if it was prior to 24 months.	0,1
Introduction of complementary foods	If the solids and semi-solid foods were introduced to the child between 6-8 months. Participants received a score of 1 if solid and semi-solid foods were introduced between 6 and 8 months of age and 0 if food was introduced below 6 months or older than 8 months.	0,1
Minimum dietary diversity	Dietary diversity was based on 24-hour recall emphasizing seven different food groups. Scores were assigned based on the number of food groups consumed. Food groups included grains, legumes, meats, eggs, vitamin A rich fruits and vegetables, other fruits and vegetables, and dairy products. The recommended minimum number of groups is 4 (25, 26). Participants received 1 if they consumed 4 or more food groups and 0 if they consumed less than 4 food groups in the past 24 hours.	0,1
Minimum meal frequency	Meal frequency was based on the previous 24 hours, including meals and snacks other than liquids. Minimum meal frequency was considered to be 2 or more meals for children age 6 to < 9 months, 3 or more meals for children ages 9 to < 12 months, and 4 or more meals for children ages 12 months and older (12). Participants received a 1 if the child received the minimum meal frequency in the previous 24 hours and a 0 if the child did not.	0,1

[1] HH, household; IYCF, Infant and young child feeding practices

Table 3.
WASH indicators from the HH survey[1]

Indicator	Definition and scoring	Range
Cleanliness of caregiver's hands	Observed cleanliness of caregiver's hands. Respondents received a score of 1 if the caregiver's hands were observed to be clean and 0 if the hands were observed to be unclean (27, 32).	0,1
Cleanliness of child's hands	Observed cleanliness of child's hands. Respondents received a score of 1 if the child's hands were observed to be clean and 0 if the hands were observed to be unclean (27, 32).	0,1
Improved water source	If drinking water comes from improved water sources. Respondents received a score of 1 if all water sources were improved sources of drinking water, and 0 if any water sources were unimproved. Improved water sources included: piped water into dwelling, piped water into yard/plot, public tap or standpipe, tube well or borehole, protected dug well, protected spring, and rainwater. Unimproved water sources included: unprotected spring, unprotected dug well, cart with small tank/drum, tanker-truck, or surface water (29).	0,1
Lids on water storage containers	If water storage containers have lids. Respondents received a score of 1 if all water storage containers were observed to have lids and 0 if any did not have lids (47).	0,1
Treat drinking water	If action is taken to treat or make the drinking water safe. Respondents were assigned a score of 1 if action was taken to make the drinking water safe for human consumption and 0 if no action was taken. Actions for making drinking water safe included: boiling, bleaching, adding chlorine, straining through a cloth, use of water filer, solar disinfection, and let it stand and settle (30).	0,1
Hand washing	Used soap or ash during a hand washing demonstration. Respondents were observed during a hand washing demonstration. If soap or ash was used during the demonstration, respondents were assigned a score of 1 and 0 if neither soap nor ash were used (27, 30).	0,1
Knowledge of critical times for caregiver hand washing	Knowledge of critical times for hand washing. The five critical times for washing hands include: 1) after defecation, 2) after cleaning a child, 3) before preparing food, 4) before feeding a child, and 5) before eating, as defined by UNICEF (30, 33). Respondents were assigned a 1 for listing all critical times points and 0 for not listing all critical time points for washing hands.	0,1

Frequency of bathing child	Number of times the enrolled child was bathed in the previous week. Respondents were assigned 0 if the child was bathed less than once per day and 1 if the child was bathed at least once per day during the previous week (34).	0,1
Improved sanitation facility	If HH uses an improved sanitation facility. Respondents received a score of 1 if HH members used an improved sanitation facility, and 0 if HH members used an unimproved sanitation facility. Improved sanitation facilities included: flush toilet, piped sewer system, septic tank, flush/pour flush to pit latrine, ventilated improved pit latrine, or pit latrine with slab. Unimproved sanitation facilities included: pit latrine without slab, bucket, hanging toilet or hanging latrine, or no facilities/bush/field (29).	0,1

[1] HH, household; WASH, water, sanitation, and hygiene.

Table 4.
Comparison of indicators regarding household characteristics, SES, IYCF practices, food security, water, sanitation, hygiene (WASH), and maternal perceptions between children who sustained recovery and all other children.[1]

	Sustained Recovery (n=180)	Those who did not sustain recovery (n=132)	*P*
HH Characteristics and SES			
Religion			0.362
Christian	133 (74)	108 (82)	
Muslim	44 (25)	23 (17)	
Other	2 (1)	1 (1)	
Other children in home diagnosed with acute malnutrition	51 (29)	32 (25)	0.419
Years of completed education by caregiver	3.89 ± 2.75	4.17 ± 2.69	0.393
Number of rooms in the house	1.87 ± 0.96	1.95 ± 1.02	0.533
Ownership of any livestock	80 (45)	68 (53)	0.501
Number of HH assets owned (out of 11 total)	3.13 ± 1.58	3.13 ± 1.64	0.999
Infant and Young Child Feeding			
Child ever breastfed	176 (99)	131 (99)	0.745
Currently breastfeeding	117 (65)	93 (71)	0.295
Appropriate timing for introduction of solid food	145 (81)	96 (74)	0.167
Meal frequency	2.86 ± 1.38	3.06 ± 1.37	0.355
Child dietary diversity score (0 to 7 food groups)	3.73 ± 1.16	3.58 ± 1.22	0.743
Food Security			
Average HFIAS score throughout one year[2]	12.55 ± 3.44	12.88 ± 3.54	0.831
Water, Sanitation, and Hygiene			
Observed cleanliness of caregiver's hands (Average score from 0 'visible dirt' to 2 'clean')	0.93 ± 0.59	0.75 ± 0.56	0.142
Observed cleanliness of child's hands (Average score from 0 'visible dirt' to 2 'clean')	1.00 ± 0.53	0.91 ± 0.55	0.530
Uses improved source for drinking water	134 (74)	90 (48)	0.225
All water storage containers have lids	78 (44)	40 (32)	0.029
Takes action to make drinking water safer	93 (52)	73 (55)	0.523
Used soap or ash during hand washing	46 (26)	30 (24)	0.788
Knowledge of all five critical times for hand washing	16 (9)	14 (11)	0.611
Number of times child was bathed during previous week	8.01 ± 3.8	7.82 ± 4.15	0.883
Uses improved sanitation facility	27 (15)	11 (8)	0.077
Caregiver Perceptions of SFP, MAM, and Relapse			

Referral source for attending SFP			0.956
Health Professional or CHW	141 (79)	105 (80)	0.868
Self	33 (18)	24 (18)	0.954
Friends or neighbors	5 (49)	3 (2)	0.774
Reason caregiver brought child to SFP			
Routine check-up	20 (23)	7 (13)	
Influence by friends or neighbors	2 (2)	1 (2)	
Child seemed ill (fever, cough, or diarrhea)	42 (48)	25 (47)	
Child seemed malnourished (appeared thin)	17 (20)	16 (30)	
Child experienced a lack of appetite	2 (2)	0 (0)	
Due to referral	4 (5)	4 (8)	
Perceived child to be sick upon admission to SFP	86 (53)	64 (54)	0.908
Perceived child to be malnourished upon admission to SFP	112 (64)	81 (64)	0.959
Perceived child's status to improve during treatment	180 (100)	132 (100)	n/a
Understood that relapse was possible	76 (42)	55 (42)	0.888
Understand that re-enrollment to SFP was possible	154 (88)	113 (86)	0.537
Understand actions could be taken to prevent MAM	150 (84)	110 (84)	0.943

[1] Values are means ± SDs, n, n (%). CHW, community health worker; HFIAS, Household Food Insecurity Access Scale (0-27); HH, household; IYCF, infant and young child feeding; MAM, moderate acute malnutrition; SES, socioeconomic status. P-values derived using student's t test or chi-squared with adjustment for clustering.

[2] HFIAS was collected at 1, 3, 6, and 12 months of follow-up. These scores were averaged to provide the food security situation at the household level at multiple points throughout the year Changes in participants' HFIAS scores between visits ranged from 0 to 23 and averaged a 10-point difference between the lowest and highest HFIAS scores across follow-up visits.

TABLE 5.
Factors associated with children who sustained recovery for twelve months following recovery from MAM in logistic regression model[1]

	Odds Ratio (95% CI)	*P*
Age (months)	1.01 (0.98, 1.05)	0.482
Female	1.61 (0.97, 2.66)	0.066
MUAC at SFP discharge (mm)	1.20 (1.09, 1.31)	< 0.001
WHZ at SFP discharge	1.12 (0.55, 1.11)	0.745
Fever in 2 weeks prior to SFP admission	0.78 (0.41, 1.49)	0.456
Diarrhea in 2 weeks prior to SFP admission	1.52 (0.70, 3.30)	0.291
Years of completed education by caregiver	0.94 (0.86, 1.02)	0.137
Number of rooms in house	0.98 (0.76, 1.27)	0.881
Ownership of any livestock[2]	0.78 (0.55, 1.11)	0.170
Number of household assets[3]	1.02 (0.85, 1.23)	0.834
Continued breastfeeding[4]	1.04 (0.36, 2.99)	0.941
Appropriate introduction of solids[5]	1.86 (0.89, 3.89)	0.098
Minimum meal frequency[6]	0.87 (0.53, 1.43)	0.577
Minimum dietary diversity[7]	0.95 (0.51, 1.77)	0.880
Average HFIAS Score[8]	0.98 (0.88, 1.09)	0.680
Water from improved water source[9]	1.45 (0.66, 3.18)	0.353
All water storage containers have lids	1.79 (1.20, 2.68)	0.004
Uses improved sanitation facility[10]	1.46 (0.95, 2.26)	0.083
Used soap or ash during handwashing demonstration	0.84 (0.29, 2.37)	0.736
Mother's hands appear "clean"[11]	2.47 (0.99, 6.18)	0.053
Child's hands appear "clean"[11]	0.65 (0.31, 1.33)	0.238
Child bathed weekly during prior 7 days	1.28 (0.67, 2.42)	0.455

[1] Logistic regression model included cluster robust standard errors to account for clustering at the health clinic level. CI, confidence interval; HFIAS, household food insecurity access scale; MUAC, mid-upper arm circumference; SES, socioeconomic status; SFP, supplementary feeding program.

[2] Livestock consists of chickens, goats, cattle, dogs, pigs, or guineafowl.

[3] The total number of assets ranges from 0 to 11, including ownership of a mattress, bicycle, cart, chair or bench, cabinet, pair of shoes, candle, lantern, torch, phone, or bank account.

[4] For ages 24 months and under, this is calculated as: if the child is currently breastfeeding. For ages over 24 months, this is calculated as: whether the child was breastfed until at 24 months.

[5]Appropriate introduction of solids is defined as introducing solid or semi-solid food between 6-8 months old.

[6] Minimum meal frequency is defined as 2 or more meals for ages 6-9 months, 3 or more meals for ages 9-12 months, and 4 or more meals for over 12 months old.

[7] Minimum dietary diversity is defined as 4 or more food groups consumed during the previous 24 hours.
[8] HFIAS was collected at 1, 3, 6, and 12 months of follow-up. These scores were averaged to provide an overall food security situation at the household level at multiple points throughout the year.
[9] Improved water sources include: Piped water into dwelling, piped water to yard/plot, public tap or standpipe, tube well or borehole, protected dug well, protected spring, rainwater, or bottled water
[10] Improved sanitation facility includes: flush toilet, piped sewer system, septic tank, flush/pour flush to pit latrine, ventilated improved pit latrine (VIP), pit latrine with slab, composting toilet, special case
[11] Cleanliness of hands were observed and scored based on "the presence of visible dirt" "a dirty appearance" or "a clean appearance" on the finger pads, finger nails, and palms.

Summary and Discussion

Summary of Findings

This research aimed to address unanswered questions regarding effective treatment for sustained recovery from MAM. The three Chapters in this dissertation present evidence regarding what happens to children following recovery from MAM as well as suggestions for future studies and improvements in the treatment practices for children suffering from MAM.

The study presented in Chapter 1 demonstrates the feasibility and effectiveness of using whey permeate and whey protein concentrate (WPC80) instead of soy flour in RUSF when treating children for MAM. The proportion of children who recovered was modestly higher among those receiving the whey RUSF in comparison with those receiving the soy RUSF. Furthermore, children who received whey RUSF showed higher MUAC gain, weight gain, discharge MUAC, and discharge WHZ than the children who received soy RUSF group. Although the two foods were not isocaloric and isonitrogenous, outcomes were better among children who received the whey RUSF despite the food providing 33% less total protein and nearly 8% less total energy than the soy RUSF. A cost-effectiveness analysis reveals that substituting whey RUSF for soy RUSF resulted in a $0.42 decrease in the cost per child recovered ($54.76 and $54.34 for soy and whey RUSF, respectively). In a hypothetical scenario with a given budget of $50,000 for total operations and food costs, using whey RUSF (as opposed to soy RUSF) would result in 3 more kids recovered than using soy RUSF. This study provides evidence that substituting whey and WPC80 for soy in RUSF leads to improved outcomes in children with MAM at only a marginal increase in food costs and a potential decrease in overall programmatic costs per child recovered. Longer-term outcomes, such as relapse and other post-discharge outcomes are explored in Chapter 2.

Results from Chapter 2 provide the first scientific evidence to show that providing additional services to a traditional SFP treatment can improve the longer-term nutrition status of children who recover from MAM. The package of services—consisting of LNS, zinc supplementation, deworming, a bed net, and malaria prophylaxis—provided at the point of discharge from an SFP, increased the proportion of children who sustained recovery for one year following initial recovery. Despite these positive results, still only 53% of children receiving the intervention sustained recovery. The strongest predictors of sustained recovery at the time of initial MAM treatment included having larger MUAC upon SFP admission, greater MUAC change between SFP admission and discharge, higher WHZ upon SFP discharge, and larger MUAC upon SFP discharge. Our results reveal that poor linear growth following SFP discharge is associated with relapse. The worst linear growth rates were associated with multiple and more severe relapses, while those who sustained recovery had the best linear growth rate. Half of all relapses occurred within the first three months of initial discharge from SFP. Nearly all levels of serum complement C3, an indicator for immune function, measured during initial recovery from MAM were found to be within the normal range.

The research presented in Chapter 3 identified household-level factors associated with sustained recovery. Results from an in-depth household (HH) survey showed that improved WASH factors, including caregivers having clean hands, HH's having fitted lids on water storage containers, and HHs that used an improved sanitation facility were associated with a child sustaining recovery for 12 months after treatment for MAM. Factors related to HH socioeconomic status, food security, and IYCF practices were not statistically different between the two groups. On an individual level, children with a higher MUAC upon discharge from initial MAM treatment in an SFP were more likely to sustain recovery than those with a lower discharge MUAC. These results suggest that interventions to improve WASH conditions may help to reduce the proportion of children who relapse following recovery from MAM; however, this is likely to be one of many other factors that must be explored in order to drastically improve the percent of children who are able to sustain recovery.

Suggestions for future research

Future studies in a variety of contexts are needed to confirm conclusions reached through this research. Also, further research is essential to generate a better understanding of potential causal pathways for associations identified in this dissertation, such as the biological role of whey and whey permeate in recovery from MAM, immune function during and following recovery from MAM, and linear growth following recovery from MAM.

Although the two treatment foods in Chapter 1 were neither isocaloric nor isonitrogenous, the whey RUSF performed better than the soy RUSF, even with lower caloric and total protein content, thus ultimately highlighting the additional benefits of whey. Still, further research is needed to identify the minimum amount of animal-based protein required to produce the best outcomes for the lowest cost. When possible, studies comparing various types of proteins should involve isocaloric and isonitrogenous foods in order to better delineate the effects of the various components in animal-based protein.

In addition to focusing on the type of food provided during treatment, future studies should examine the effect of distinct treatment protocols for children at higher risk for not sustaining recovery following MAM. For example, this might include assessing the effectiveness and cost-effectiveness of SFPs that provide additional support to children who present for treatment with lower MUAC and no reports of illness, as these were identified as predictive of relapse. Additional clinical trials are warranted that examine various SFP discharge criteria, such as higher MUAC cut-offs, and their impact on sustained recovery. Also needed are studies to identify the biological differences between children who sustain recovery and those that do not. For example, investigations should explore potential causal pathways between poor WASH conditions and relapse, including the possible role that environmental enteric dysfunction and other underlying infections may play. Given the associations between poor linear growth and relapse after MAM, follow-up studies that focus on improving the effectiveness of MAM treatment should also include a longer term outcomes, such as linear growth, development, co-morbidities, and relapse following discharge.

Policy implications

This research suggests that a uniform approach for treating all children with MAM may not be appropriate to achieve sustained recovery. Children presenting to SFP with identified risk factors of relapse, particularly lower MUAC upon admission, may need additional care and post-discharge follow-up to prevent relapse. Also, raising the

MUAC cut-off for discharge for those with identified risk factors of relapse may be necessary to prevent relapse in the subsequent year after recovery. Although our results showed improved outcomes during initial recovery for children who received a whey-based RUSF compared to those who received a soy-based RUSF, the type of food consumed during treatment did not seem to have an effect on post-discharge outcomes, including relapse, mortality, illness, or linear growth.

Secondly, our results suggest that the current definition of recovery from MAM may need to be revised. Given the association between higher MUAC upon SFP discharge and sustained recovery, it may be necessary to increase the current MUAC discharge criterion from 12.5 cm to higher cut-off, such as 13.0 or 13.5 cm. Future clinical trials would need to confirm if an increase would indeed improve the proportion of children who achieve sustained recovery and what how much of an increase is most appropriate. Furthermore, the additional cost of treating children to a higher MUAC discharge criterion (presumably with lower relapse rates) must be compared with the costs saved by reducing the number of SFP readmissions required to treat episodes of relapse.

A better understanding of the relationship between accretion of muscle versus fat mass during the treatment of MAM may be a critical step in understanding how to improve sustained recovery. While MUAC is associated with both muscle and fat mass, it does not distinguish between those who increase muscle mass as a percent of total lean body and those who simply gain fat mass. The ability to increase muscle mass in relationship with sustained recovery should be closely examined in future studies and taken into consideration when determining the definition of MAM recovery.

Third, a more holistic view of recovery, beyond a certain threshold in weight, from MAM is needed. Treatment should not be confined to a short provision of food that results in a temporary weight gain; rather, SFP programs should collaborate with other child health services that can provide appropriate nutrition counseling, continued growth monitoring after discharge, HIV-related services, and other types of preventive care after SFP discharge to facilitate sustained recovery. Given the high amount of relapses and illness that occur within the first three months after initial discharge from SFP, our results suggest possible underlying physiological factors may not have fully recovered at the time of discharge, leaving the child susceptible to relapse. Therefore, continued access to health facilities and interventions that reduce the acquisition of new infections and provide appropriate treatment for illness could reduce the likelihood that children relapse. Also, policy and programs should consider nutrition-sensitive interventions that improve WASH practices to coincide with SFPs, which may reduce the likelihood of relapse following recovery from MAM.

Lastly, our results reiterate the importance of early identification of children with acute malnutrition. Given that those with more severe malnutrition (identified by lower MUAC) upon admission to SFPs are at greater risk for relapse, increased community engagement with active case finding to identify and treat children with MAM as early as possible may reduce the high post-discharge relapse and mortality rate. Integrating MUAC screening as a priority in community-based health and nutrition programing is essential. Furthermore, providing MUAC tapes and educating caregivers on how to monitor their own children's MUAC could also greatly improve earlier identification of acute malnutrition.

Appendices

Appendix 1. Data Collection Cards for Whey Permeate Study (Chapter 1)

ST. LOUIS NUTRITION PROJECT **Whey Permeate** STUDY

STUDY ID: ____________

CHILD'S NAME: ____________ **MALE / FEMALE**

SITE: ____________ **DATE OF BIRTH:** ____________ (dd/mm/yy) **Study Food: RED or BLUE**

WEEK	DATE (dd/mm/yy)	LENGTH (cm)	WEIGHT (kg)	MUAC (cm)	EDEMA	KUTENTHA THUPI (FEVER) (masiku angati)	KUTSEGULA M'MIMBA (DIARRHEA) (masiku angati)	RASH (masiku angati)	Bottles of Study Food Left?	Eating Food Well?	HEALTH CENTER VISIT/ MEDS	COMMENTS (about symptoms/meds/health center/compliance)	# bottles given
**Start		1 2 3			Y / N +1 +2 +3					Y / N	Y / N		
2		1 2 3			Y / N +1 +2 +3					Y / N	Y / N		
4		1 2 3			Y / N +1 +2 +3					Y / N	Y / N		
6		1 2 3			Y / N +1 +2 +3					Y / N	Y / N		
8		1 2 3			Y / N +1 +2 +3					Y / N	Y / N		
10		1 2 3			Y / N +1 +2 +3					Y / N	Y / N		
12		1 2 3			Y / N +1 +2 +3					Y / N	Y / N		

Missed: 1) ______ / ______ / ______ Sent the message? *Y / N*. **2)** ______ / ______ / ______ Sent the message? *Y / N*. **3)** ______ / ______ / ______ Home visit completed? *Y / N*.

OUTCOME: GRADUATE TRANSFER TO HOSPITAL TRANSFER TO RUTF (SAM) TRANSFER TO RUTF (12 WEEKS) MISSED 3 CONSECUTIVE VISITS DEATH

St. Louis Nutrition Project - Whey Permeate Study

Food Frequency Questionnaire

	2X/DAY	1X/DAY	3X/WEEK	2X/WEEK	1X/WEEK	2X/MONTH	1X/MONTH	2X/YEAR	1X/YEAR	Never
Cow's Milk										
Goat's Milk										
Milk Powder										
Butter										
Cheese										
Yogurt										
Ice cream										

Household Food Insecurity Access Scale (HFIAS) Measurement Tool

Name of survey administrator:____

Date:____________________________

No.	Question	Coding	Answer
1	In the past four weeks, did you worry that your household would not have enough food?	0 = No If yes, How frequently did this happen? 1 = Rarely (once or twice) 2 = Sometimes (three to ten times) 3 = Often (more than ten times)	|___|
2	In the past four weeks, were you or any household member not able to eat the kinds of foods you preferred because of a lack of resources?	0 = No If yes, How frequently did this happen? 1 = Rarely (once or twice) 2 = Sometimes (three to ten times) 3 = Often (more than ten times)	|___|
3	In the past four weeks, did you or any household member have to eat a limited variety of foods due to a lack of resources?	0 = No If yes, How frequently did this happen? 1 = Rarely (once or twice) 2 = Sometimes (three to ten times) 3 = Often (more than ten times)	|___|
4	In the past four weeks, did you or any household member have to eat some foods that you really did not want to eat because of a lack of resources to obtain other types of food?	0 = No If yes, How frequently did this happen? 1 = Rarely (once or twice) 2 = Sometimes (three to ten times) 3 = Often (more than ten times)	|___|
5	In the past four weeks, did you or any household member have to eat a smaller meal than you felt you needed because there was not enough food?	0 = No If yes, How frequently did this happen? 1 = Rarely (once or twice) 2 = Sometimes (three to ten times) 3 = Often (more than ten times)	|___|
6	In the past four weeks, did you or any household member have to eat fewer meals in a day because there was not enough food?	0 = No If yes, How frequently did this happen? 1 = Rarely (once or twice) 2 = Sometimes (three to ten times) 3 = Often (more than ten times)	|___|

7	In the past four weeks, was there ever no food to eat of any kind in your household because of lack of resources to get food?	0 = No If yes, How frequently did this happen? 1 = Rarely (once or twice) 2 = Sometimes (three to ten times) 3 = Often (more than ten times)	|___|
8	In the past four weeks, did you or any household member go to sleep at night hungry because there was not enough food?	0 = No If yes, How frequently did this happen? 1 = Rarely (once or twice) 2 = Sometimes (three to ten times) 3 = Often (more than ten times)	|___|
9	In the past four weeks, did you or any household member go a whole day and night without eating anything because there was not enough food?	0 = No If yes, How frequently did this happen? 1 = Rarely (once or twice) 2 = Sometimes (three to ten times) 3 = Often (more than ten times)	|___|

Appendix 2. Data Collection Cards for Moderate Follow-up Study (Chapter 2)

St. Louis Nutrition Project -- MODERATE FOLLOW-UP STUDY

STUDY ID: ____________________

CHILD'S NAME: ________________________________ MALE / FEMALE

Moderate ID (if different): ____________________

SITE: ______________________________ DATE OF BIRTH: ____________________ (dd/mm/yy)

CONTROL or INTERVENTION (circle one) Albendazole __________ Zinc __________ LNS #1 __________ #2 __________ Malaria #1 __________ #2 __________ #3 __________ Mosq Net __________

Month Visit #	DATE (dd/mm/yy)	LENGTH (cm)	WEIGHT (kg)	MUAC (cm)	EDEMA	KUTENTHA THUPI (FEVER) (masiku angati)	KUTSEGULA M'MIMBA (DIARRHEA) (masiku angati)	RASH (masiku angati)	Eating Food Well?	HEALTH CENTER VISIT / MEDS	COMMENTS (about symptoms/meds/health center/compliance)
Grad					Y / N +1 +2 +3				Y / N	Y / N	
					Y / N +1 +2 +3				Y / N	Y / N	
					Y / N +1 +2 +3				Y / N	Y / N	
					Y / N +1 +2 +3				Y / N	Y / N	
					Y / N +1 +2 +3				Y / N	Y / N	
					Y / N +1 +2 +3				Y / N	Y / N	
					Y / N +1 +2 +3				Y / N	Y / N	
					Y / N +1 +2 +3				Y / N	Y / N	
					Y / N +1 +2 +3				Y / N	Y / N	
					Y / N +1 +2 +3				Y / N	Y / N	
					Y / N +1 +2 +3				Y / N	Y / N	
					Y / N +1 +2 +3				Y / N	Y / N	

Missed: 1) ______/______/______ Sent the message? Y / N. 2) ______/______/______ Sent the message? Y / N. 3) ______/______/______ Home visit completed? Y / N. Notes: ____________________

Missed: 1) ______/______/______ Sent the message? Y / N. 2) ______/______/______ Sent the message? Y / N. 3) ______/______/______ Home visit completed? Y / N. Notes: ____________________

OUTCOME: REMAINED WELL TRANSFER TO HOSPITAL SAM MAM MISSED 3 CONSECUTIVE VISITS DEATH

ST. LOUIS NUTRITION PROJECT MODERATE FOLLOW-UP STUDY *RELAPSE CARD*

STUDY ID: ____________________

CHILD'S NAME: ______________________________ **MALE / FEMALE**

SAM

SITE: ____________________ **DATE OF BIRTH:** ____________________ (dd/mm/yy) **MAM**

Week	DATE (dd/mm/yy)	LENGTH (cm)		WEIGHT (kg)	MUAC (cm)	EDEMA	KUTENTHA THUPI (FEVER) (masiku angati)	KUTSEGULA M'MIMBA (DIARRHEA) (masiku angati)	RASH (masiku angati)	Bottles of Study Food Left?	Eating Food Well?	HEALTH CENTER VISIT / MEDS	COMMENTS (about symptoms/meds/health center/compliance)	# bottles given
		1				Y / N								
**Start		2									Y / N	Y / N		
		3				+1 +2 +3								
		1				Y / N								
2		2									Y / N	Y / N		
		3				+1 +2 +3								
		1				Y / N								
4		2									Y / N	Y / N		
		3				+1 +2 +3								
		1				Y / N								
6		2									Y / N	Y / N		
		3				+1 +2 +3								
		1				Y / N								
8		2									Y / N	Y / N		
		3				+1 +2 +3								
		1				Y / N								
10		2									Y / N	Y / N		
		3				+1 +2 +3								
		1				Y / N								
12		2									Y / N	Y / N		
		3				+1 +2 +3								

Missed: 1) ______ / ______ / ______ Sent the message? *Y / N.* **2)** ______ / ______ / ______ Sent the message? *Y / N.* **3)** ______ / ______ / ______ Home visit completed? *Y / N.*

OUTCOME: GRADUATE TRANSFER TO HOSPITAL TRANSFER TO RUTF (SAM) TRANSFER TO RUTF (12 WEEKS) MISSED 3 CONSECUTIVE VISITS DEATH

Health History Questionnaire

1. Caretaker name (dzina la wo yan'ganira mwana): ________________________________
2. What immunizations has the child received?
   ____
3. Does the child sleep under a bed net? Yes / No
4. Does the child take malaria prophylaxis? Yes / No
5. Does the child take any other medication? Yes / No
   a. If yes, what other medications does the child take? _____________________________________
6. Does the child take any supplements (vitamin/mineral)? Yes / No
   a. If yes, what kind? ____
7. Does the child receive deworming medication? Yes / No
   a. Has your child received deworming medication in the last month?
      ____
8. Village _____________________________Community Health Worker _____________________________
   a. Directions to village:
      ____
      ____
      ____
9. Phone Number. ___________________________________

Appendix 3. In-depth Household Survey (Chapter 3)

St. Louis Nutrition Project
Moderate Malnutrition Follow-Up Study
Household Survey

To be completed at SFP clinic:

Z1 Child ID ______________________________

Z2 Child Name ______________________________

Z3 Respondent Name (Caregiver) ______________________________

Z4 Site/Health Center ______________________________

Z5 Interviewer Name ______________________________

Z6 Observe Child and Caregiver Hands:

Coding		
1 = Visible dirt	**a.** Child's Palm's	|_____|
2 = Unclean appearance	**b.** Child's Finger Pads	|_____|
3 = Clean	**c.** Child's Finger Nails	|_____|
	d. Caregiver's Palm's	|_____|
	e. Caregiver's Finger Pads	|_____|
	f. Caregiver's Finger Nails	|_____|

Village: ______________________________ Directions to home: ______________________________

____

____

____

____

Transportation cost from H/C to caregiver home: __________ MKW

Scheduled Home-Visit Date: ______ / ______ / ______
Day Month Year

Upon Arrival at Home-Visit:

When you arrive at the caregiver's home, please introduce yourself and St. Louis Nutrition Project. Remind her that she agreed to participate in the research that St. Louis is conducting. As part of the research, she schedule this home-visit.

A DEMOGRAPHICS & SES

We want to collect some general information about everyone in this household. A household is a group of people who normally eat their meals together.

#	QUESTION	CODING	ANSWER	GO TO
A1	Is the caregiver the mother?	1 = yes 2 = no	|____|	***If 1 --> A3***
A2	If not, what is the relationship between the caregiver and (NAME)? Other (specify) ___________________________________	1 = grandmother 2 = aunt 3 = sister 4 = other relative 5 = neighbor 6 = other	|____|	***If 6 --> Other (specify)***
A3	What is the primary religion of the household? Other (specify) ___________________________________	1 = Christian 2 = Muslim 3 = Animist 4 = Other	|____|	***If 4 --> Other (specify)***
A4	Have any children other than (NAME), in the household ever been diagnosed as malnourished?	1 = yes 2 = no	|____|	***If 2 --> A6***
A5	If yes, how many?	*Write in number*	|____|	
A6	What is caregiver's highest level of education?	0 = no schooling 8 = Standard 8 1 = Standard 1 9 = Form 1 2 = Standard 2 10 = Form 2 3 = Standard 3 11 = Form 3 4 = Standard 4 12 = Form 4 5 = Standard 5 13 = Higher 6 = Standard 6 Education 7 = Standard 7 99 = Don't know	|____|	
A7	How many people live in this house?	*Write in number*	|____|	
A8	How many separate rooms does this house have?	*Write in number*	|____|	
A9	Do you have a separate room that is used as a kitchen?	1 = yes 2 = no	|____|	
A10	Does your household own any of the following in working condition?			
	a. mattress	1 = yes 2 = no	**a |___|**	
	b. bicycle	1 = yes 2 = no	**b |___|**	
	c. motorcycle, car, or truck	1 = yes 2 = no	**c |___|**	
	d. animal-drawn cart	1 = yes 2 = no	**d |___|**	
	e. chair or bench	1 = yes 2 = no	**e |___|**	
	f. radio	1 = yes 2 = no	**f |___|**	
	g. mobile phone	1 = yes 2 = no	**g |___|**	
	h. torch	1 = yes 2 = no	**i |___|**	
	i. cupboard/cabinet	1 = yes 2 = no	**j |___|**	
	j. shoes	1 = yes 2 = no	**k |___|**	
	k. candle	1 = yes 2 = no	**l |___|**	
	l. lantern	1 = yes 2 = no	**m |___|**	
A11	Does any member of this household have a bank account?	1 = yes (traditional bank or community banking group) 2 = no	|____|	
A12	Does anyone in your household own any agricultural land?	1 = yes 2 = no	|____|	***If 2 --> C1***
A13	How many bags of harvest do you collect?	*Write in number*	|____|	

C. YOUNG CHILD FEEDING PRACTICES AND CHILD DIETARY DIVERSITY				
#	**QUESTION**	**CODING**	**ANSWER**	**GO TO**
C1	Has (NAME) ever been breastfed?	1 = yes, 2 = no, 99 = Don't Know	|___|	***If 2-->C5*** ***If 99 --> C5***
C2	Is (NAME) currently breastfeeding?	1 = yes, 2 = no, 99 = Don't Know	|___|	***If 2-->C4*** ***If 99 --> C4***
C3	Now I would like you to tell me how many times (NAME) breastfed yesterday. I am going to read you some answers and I want you to please tell me which you think is closest. ***(Read ALL choices. Then tick which the respondent says is most true.)***	0 = Not at all. 1 = Only at night. 2 = Very little, only 1 or 2 times during the day. 3 = Moderately, about 3 to 5 time during the day. 4 = Very often, at least 6 times during the day. 99 = Don't know.	|___|	
C4	How old was (NAME) when she/he last breastfed?	*Write in age in months*	|___|	
C5	How old was (NAME) when she/he first ate semi-solid, solid, or soft foods?	*Write in age in months*	|___|	
C6	How many times did (NAME) eat solid, semi-solid, or soft foods other than liquids yesterday during the day and at night?	*Write in number*	|___|	

D1. CHILD DIETARY DIVERSITY

This section pertains to the child enrolled in the study.

Please describe everything (NAME) ate yesterday during day and night, whether at home or outside the home.

a Think about when (NAME) first woke up yesterday. Did (NAME) eat anything at that time? If yes, please tell me everything (NAME) ate at that time. ***Record answers in the box below:***

Probe: Anything else? ***Record answers in the box above.***

If respondent mentions mixed dishes like a porridge, sauce or stew, probe: What ingredients were in that (mixed dish)?

b What did (NAME) do after that? Did (NAME) eat anything at that time? If yes: Please tell me everything (NAME) ate at that time. ***Probe:*** Anything else? ***Record what was eaten in the box below:***

Probe: *Anything else****? Record answers in the box above.***

If respondent mentions mixed dishes like a porridge, sauce or stew, probe: *What ingredients were in that (mixed dish)?*

c What did (NAME) do after that? Did (NAME) eat anything at that time? If yes: Please tell me everything (NAME) ate at that time. ***Probe:*** Anything else? ***Record what was eaten in the box below:***

Probe: *Anything else****? Record answers in the box above.***

If respondent mentions mixed dishes like a porridge, sauce or stew, probe: *What ingredients were in that (mixed dish)?*

d What did (NAME) do after that? Did (NAME) eat anything at that time? If yes: Please tell me everything (NAME) ate at that time. Probe: Anything else? Record what was eaten in the box below:

Probe: *Anything else****? Record answers in the box above.***

If respondent mentions mixed dishes like a porridge, sauce or stew, probe: *What ingredients were in that (mixed dish)?*

e Was there anything else that (NAME) ate from that point on until (NAME) fell asleep at night? If yes: Please tell me (NAME) ate everything that time. ***Record what was eaten in the box below:***

Probe: Anything else? Record answers in the box above.

If respondent mentions mixed dishes like a porridge, sauce or stew, probe: *What ingredients were in that (mixed dish)?*

D. CHILD DIETARY DIVERSITY This section pertains to the child enrolled in the study.			
D2	Now I am going to list different groups of food. Please tell me if (NAME) ate or drank any food in each group.		
a.	Group 1: Nsima, porridge, bread, rice, noodles ,millet, sorghum or other foods made from grains	1 = yes, 2 = no	**a.** |___|
b.	Group 2: Pumpkin, carrots, squash, or sweet potatoes that are yellow or orange inside	1 = yes, 2 = no	**b.** |___|
c.	Group 3: White potatoes, white yams, manioc, cassava, or any other foods made from roots	1 = yes, 2 = no	**c.** |___|
d.	Group 4: Any dark green leafy vegetables	1 = yes, 2 = no	**d.** |___|
e.	Group 5: Ripe mangoes, ripe papayas,	1 = yes, 2 = no	**e.** |___|
f.	Group 6: Any other fruits or vegetables (such as tomato)	1 = yes, 2 = no	**f.** |___|
g.	Group 7: Liver, kidney, heart, or other organ meats	1 = yes, 2 = no	**g.** |___|
h.	Group 8: Any meat, such as beef, pork, lamb, goat, chicken, or duck	1 = yes, 2 = no	**h.** |___|
i.	Group 9: Eggs	1 = yes, 2 = no	**i.** |___|
j.	Group 10: Fresh or dried fish, shellfish, or seafood	1 = yes, 2 = no	**j.** |___|
k.	Group 11: Any foods made from beans, peas, lentils, nuts, or seeds	1 = yes, 2 = no	**k.** |___|
l.	Group 12: Cheese, yogurt, or other milk products	1 = yes, 2 = no	**l.** |___|
m.	Group 13: Any oil, fats, or butter, or foods made with any of these	1 = yes, 2 = no	**m.**|___|
n.	Group 14: Any sugary foods such as chocolates, sweets, candies, pastries, cakes, or biscuits	1 = yes, 2 = no	**n.** |___|
o.	Group 15: Condiments for flavor, such as chilies, spices, herbs, or fish powder	1 = yes, 2 = no	**o.** |___|
p.	Group 16: Grubs, snails, or insects	1 = yes, 2 = no	**p.** |___|
q.	Group 17: Foods made with red palm oil, red palm nut, or red palm nut pulp sauce	1 = yes, 2 = no	**q.** |___|

F. WATER SANITATION AND HYGIENE PRACTICES				
#	**QUESTION**	**CODING**	**ANSWER**	**GO TO**
F1	Where does your household usually fetch drinking water? (***Tick up to three. If more then three, ask them which three they mostly fetch drinking water from.)***	1 = piped water into dwelling 2 = piped water into yard/plot 3 = public tap or pipestand 4 = tube well or borehole 5 = dug well (protected) 6 = dug well (unprotected) 7 = rainwater 8 = tanker truck 9 = surface water (river/dam/lake/pond/stream/ irrigation channel) 10 = bottled water 11 = other Other (specify) ___________________	|___| |___| |___|	***If 11 --> Specify***
F2	How many times per day does someone in your household go to fetch water?	*Write in number of times*	|___|	
F3	Can you please show me the container(s) you usually store drinking water? ***Observe: Does the container have a lid or fitted cover.***	1 = yes, all of them have lids 2 = some of them have lids 3 = no, none of them have lids	|___|	
F4	Do you do anything to the water to make it safer to drink?	1 = yes 2 = no	|___|	***If 2 --> F12***
F5	What do you usually do to make the water safer to drink? ***(List up to 3 main responses)***	1 = Boil 2 = Add bleach/chlorine 3 = Strain through a cloth 4 = Use water filter (ceramic/sand/composite/etc.) 5 = Solar disinfection 6 = Let it stand and settle 7 = Other Other (specify) ____________________	|___| |___| |___|	***If 7 --> Specify***
F6	Can you show me how you usually clean your hands? Please do this as you would if I were not here.	1 = demonstrated 2 = not demonstrated	|___|	***If 2 --> F16***
	Observe: Were the following items used during the demonstration?			
F7	***F7. Water***	1 = yes, 2 = no	|___|	
F8	***F8. Soap***	1 = yes, 2 = no	|___|	
F9	***F9. Other***	1 = yes, 2 = no Other (specify) ____________________	|___|	

#	QUESTION		CODING	ANSWER	GO TO
F10	In what situations do you wash your hands? **(Do not read the answers. Tick all responses mentioned. If the respondent indicates that she does not know, do not give example responses. When respondent stops giving responses, probe again if there is anything else.)**	a. Before eating b. After eating c. Before breastfeeding d. Before feeding child e. Before cooking or preparing food f. After defecation/urination g. After cleaning a child that has defecated/changing a child's nappy h. When my hands are dirty i. After cleaning the toilet or latrine j. After contact with animals k. After contact with animal feces l. After farming m. After cleaning house/sweeping n. Does not know o. before and after prayers p. Other Other (specify) ___________________________	Mark "1" if mentioned	**a.** |___| **b.** |___| **c.** |___| **d.** |___| **e.** |___| **f.** |___| **g.** |___| **h.** |___| **i.** |___| **j.** |___| **k.** |___| **l.** |___| **m.** |___| **n.** |___| **o.** |___| **p.** |___|	***If 1 --> Other (specify)***
F11	In what situations do you wash (NAME'S) hands? ***(Do not read the answers. Tick all responses mentioned. If the respondent indicates that she does not know, do not give example responses. When respondent stops giving responses, probe again if there is anything else.)***	a. Before (NAME) eats b. After (NAME) eats c. Before breastfeeding (NAME) d. After (NAME) defecates/urinates e. When (NAME)'s hands are dirty f. After contact with animal feces g. After contact with animals h. When I bathe (NAME) i. Does not know j. Other Other (specify) ___________________________	Mark "1" if mentioned	**a.** |___| **b.** |___| **c.** |___| **d.** |___| **e.** |___| **f.** |___| **g.** |___| **h.** |___| **i.** |___| **j.** |___|	***If 1 --> Other (specify)***

#	QUESTION	CODING	ANSWER	GO TO
F12	How many times in the past 7 days was the child bathed?	*Write in number of times*	|___|	
F13	What kind of toilet facility do members of your household usually use? ***(If possible observe latrine to confirm)***	1 = no facility/bush/field 2 = Pit latrine without slab/open pit 3 = Pit latrine with slab 4 = Bucket toilet 5 = Ventilated improved pit latrine 6= Flush toilet or pour toilet 7 = Composting toilet 8 = Other Other (specify) ____________________	|___|	***If 8 --> Other (specify)***

G. HOUSEHOLD ENVIRONMENT

This section pertains to the entire household

Ask each of the questions G1-G3 and mark the corresponding answers for each of the different animals.										
G1. How many of the following livestock/ animals does your household own?				**G2.** Are any of these animals kept in an enclosed animal pen or gate?			**G3.** Do any of these animals come inside the house?			
	CODING	**ANSWER**	**GO TO**		**CODING**	**ANSWER**		**CODING**	**ANSWER**	
a. Chickens	*Write in number*	|____|	***If all 0 --> G4***	**a.** Chickens	1 = yes, 2 = no	|____|	**a.** Chickens	1 = yes, 2 = no	|____|	
b. Goats		|____|		**b.** Goats	1 = yes, 2 = no	|____|	**b.** Goats	1 = yes, 2 = no	|____|	
c. Dogs		|____|		**c.** Dogs	1 = yes, 2 = no	|____|	**c.** Dogs	1 = yes, 2 = no	|____|	
d. Cattle		|____|		**d.** Cattle	1 = yes, 2 = no	|____|	**d.** Cattle	1 = yes, 2 = no	|____|	
e. Pigs		|____|		**e.** Pigs	1 = yes, 2 = no	|____|	**e.** Pigs	1 = yes, 2 = no	|____|	
f. Donkey		|____|		**f.** Donkey	1 = yes, 2 = no	|____|	**f.** Donkey	1 = yes, 2 = no	|____|	
g. Guinea fowl		|____|		**g.** Guinea fowl	1 = yes, 2 = no	|____|	**g.** Guinea fowl	1 = yes, 2 = no	|____|	
h. Other		|____|		**h.** Other	1 = yes, 2 = no	|____|	**h.** Other	1 = yes, 2 = no	|____|	

#	QUESTION	CODING	ANSWER	GO TO
G4	In the past 14 days, have you seen (NAME) have any feces on his/her hands, mouth, or face?	1 = Yes 2 = No	|___|	
G5	Is the cooking usually done in the house, in a separate building, or outdoors?	1 = inside the house 2 = in separate building 3 = outdoors	|___|	
G6	Do you have an insecticide treated bed net in your house?	1 = Yes 2 = No	|___|	***If 2--> J1***
G7	If yes, can you show it to me? ***(Observe the condition of the net)***	1 = hanging in bedroom 2 = not hanging in bedroom	|___|	
G8	Did anyone in the household sleep under a net last night?	1 = Yes 2 = No	|___|	***If 2 --> J1***
G9	If yes, who? (***Tick all that apply)*** **a.** the child enrolled in study **b.** other children under 5 **c.** older children **d.** adults	 1 = yes, 2 = no 1 = yes, 2 = no 1 = yes, 2 = no 1 = yes, 2 = no	 **a.** |___| **b.** |___| **c.** |___| **d.** |___|	

J. PERCEPTIONS OF MAM, SFP, AND RELAPSE This section pertains to the caregiver only.				
#	**QUESTION**	**CODING**	**ANSWER**	**GO TO**
J1	How were you referred to the Feeding Clinic/SFP? Other (specify) ____________________	1 = HSA/clinician/nurse/volunteer 2 = self 3 = other	|___|	***If 3 --> Specify***
J2	What was your reasoning for bringing (NAME) to the SFP? Other (specify) ____________________	1 = routine check-up/assessment 2 = because other women, friends, neighbors do it or told me too 3 = child seemed ill (fever, cough, diarrhea) 4 = child seemed malnourished (thin) 5 = lack of appetite 6 = I was referred by someone 7 = other	|___|	***If 3 --> J4 If 4 --> J6 If 7 --> Specify***
J3	At the time of admission to the SFP, did you perceive (NAME) to be sick?	1 = yes 2 = no	|___|	***If 2 --> J5***
J4	If yes, what made you think (NAME) was sick? ____________________			
J5	At the time of admission to the SFP, did you perceive (NAME) to be malnourished?	1 = yes 2 = no	|___|	***If 2 --> J7***
J6	If yes, what made you think (NAME) was malnourished? ____________________			
J7	Over the course of treatment, did you perceive (NAME)'s health or nutrition status to be changing?	1 = yes 2 = no	|___|	***If 2 --> J9***
J8	If yes, what things about the child made you think this? ____________________			
J9	Can you explain all the things you were instructed on at the SFP clinic? (***Do NOT READ choices. Tick all that are mentioned).***			
	a. How to recognize if my child is malnourished	1 = yes 2 = no	**a.** |___|	
	b. How to feed the Chiponde to my child	1 = yes 2 = no	**b.** |___|	
	c. What foods to feed to my child	1 = yes 2 = no	**c.** |___|	
	d. How to recognize when my child is so ill that he needs to be taken to the hospital	1 = yes 2 = no	**d.** |___|	
	e. Washing hands with soap and water	1 = yes 2 = no	**e.** |___|	
	f. How to give the medication to my child	1 = yes 2 = no	**f.** |___|	
	g. What a mosquito net is and how to use it	1 = yes 2 = no	**g.** |___|	
	h. When to come back for follow-up	1 = yes 2 = no	**h.** |___|	
	i. Other Other (specify)____________________		**i.** |___|	***If 1--> Specify***

J10	At the end of (NAME)'s treatment and (NAME) was declared to be healthy, did you think that (NAME) could become malnourished again in the future?	1 = yes 2 = no	|___|	
J11	Were you aware that you could re-enroll (NAME) for further treatment if (NAME) becomes malnourished again?	1 = yes 2 = no	|___|	
J12	Do you think there is anything you could do to prevent (NAME) from becoming malnourished again?	1 = yes 2 = no	|___|	***If 2 --> End***
J13	If yes, what? ***(Do NOT read choices. Tick all that are mentioned)***			
	a. Continue breastfeeding my child	1 = yes 2 = no	**a.** |___|	
	b. Provide my child with a variety of foods	1 = yes 2 = no	**b.** |___|	
	c. Provide my child with more ground nuts	1 = yes 2 = no	**c.** |___|	
	d. Feed my child several times a day	1 = yes 2 = no	**d.** |___|	
	e. Wash my hands and the child with soap and water	1 = yes 2 = no	**e.** |___|	
	f. Immediately take my child to the hospital when s/he has a severe illness	1 = yes 2 = no	**f.** |___|	
	g. Bring child to clinic for routine assessment	1 = yes 2 = no	**g.** |___|	
	h. Use bednets	1 = yes 2 = no	**h.** |___|	
	i. Other	1 = yes 2 = no	**i.** |___|	***If 1--> Specify***
	Other (specify)_____________________________________			

Thank you so much for your time and patience with this interview. Before we end, is there anything you would like to add? If you have any questions for me I will be glad to respond.

Fill out and provide the caregiver with a "Completed Interview Card". Be sure to write the study ID, date of interview, and your name (interviewer)
Please ask to see the small appointment card. Look at the date of the caregiver's next clinic visit. Remind them to go to clinic at that time.

Here is a card that indicates that you completed this interview. Bring this to your next appointment at the feeding clinic and you will receive a small gift for completing this interview.

Z7 End time (use 24 hour clock, HH:MM) |______| : |______|