Effect of Preventive Supplementation With Ready-to-Use Therapeutic Food on the Nutritional Status, Mortality, and Morbidity of Children Aged 6 to 60 Months in Niger: A Cluster Randomized Trial

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Wasting (weight-for-height z score [WHZ] < −2 of the National Center for Health Statistics [NCHS] reference median) affects approximately 10% of the world’s children younger than 5 years and is an important contributor to the population-attributable risk of child mortality and overall burden of disease. New outpatient and community-based models for the treatment of wasting have been shown effective in the rehabilitation of children with severe wasting. These models are made possible largely with the use of ready-to-use therapeutic foods (RUTFs). These foods are energy-dense, micronutrient-enriched pastes with a nutritional profile similar to the traditional F-100 milk-based diet used in inpatient therapeutic feeding programs and are often made up of peanuts, oil, sugar, and milk powder.

Ready-to-use therapeutic food has been shown effective in the treatment of severe and moderate wasting and was associated with higher recovery and reduced mortality. However, their effectiveness in the population-based prevention of moderate and severe wasting has not been evaluated.

Objective To evaluate the effect of a 3-month distribution of RUTF on the nutritional status, mortality, and morbidity of children aged 6 to 60 months in Niger.

Design, Setting, and Participants A cluster randomized trial of 12 villages in Maradi, Niger. Six villages were randomized to intervention and 6 to no intervention. All children in the study villages aged 6 to 60 months were eligible for recruitment.

Intervention Children with weight-for-height 80% or more of the National Center for Health Statistics reference median in the 6 intervention villages received a monthly distribution of 1 packet per day of RUTF (92 g [500 kcal/d]) from August to October 2006. Children in the 6 nonintervention villages received no preventive supplementation. Active surveillance for conditions requiring medical or nutritional treatment was conducted monthly in all 12 study villages from August 2006 to March 2007.

Main Outcome Measures Changes in weight-for-height z score (WHZ) according to the World Health Organization Child Growth Standards and incidence of wasting (WHZ < −2) over 8 months of follow-up.

Results The number of children with height and weight measurements in August, October, December, and February was 3166, 3110, 2936, and 3026, respectively. The WHZ difference between the intervention and nonintervention groups was −0.10 (95% confidence interval [CI], −0.23 to 0.03) at baseline and 0.12 (95% CI, 0.02 to 0.21) after 8 months of follow-up. The adjusted effect of the intervention on WHZ from baseline to the end of follow-up was thus 0.22 (95% CI, 0.13 to 0.30). The absolute rate of wasting and severe wasting, respectively, was 0.17 events per child-year (140 events/841 child-years) and 0.03 events per child-year (29 events/943 child-years) in the intervention villages, compared with 0.26 events per child-year (233 events/895 child-years) and 0.07 events per child-year (71 events/1029 child-years) in the nonintervention villages. The intervention thus resulted in a 36% (95% CI, 17% to 50%; P < .001) reduction in the incidence of wasting and a 58% (95% CI, 43% to 68%; P < .001) reduction in the incidence of severe wasting. There was no reduction in mortality, with a mortality rate of 0.007 deaths per child-year (7 deaths/986 child-years) in the intervention villages and 0.016 deaths per child-year (18 deaths/1099 child-years) in the nonintervention villages (adjusted hazard ratio, 0.51; 95% CI, 0.25 to 1.05).

Conclusion Short-term supplementation of nonmalnourished children with RUTF reduced the decline in WHZ and the incidence of wasting and severe wasting over 8 months.

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The effectiveness of RUTF in the population-based prevention of moderate and severe wasting in children has not been previously evaluated.

Using data collected in a cluster randomized trial, this study aimed to assess the effect of a 3-month distribution of RUTF to nonmalnourished children in a region with traditionally high levels of child malnutrition. A cluster randomized trial, with the village as the unit of randomization, was used given the study’s aim to evaluate the effectiveness of a population-based, preventive distribution of RUTF delivered at the village rather than the individual level. The primary hypotheses were that village-level supplementation with RUTF in the months preceding the annual harvest would prevent declines in individual weight-for-height and reduce the incidence of wasting in children aged 6 to 60 months over a period of 8 months. Because RUTF may have additional health effects, the intervention effect on individual height-for-age, stunting, mortality, and morbidity from malaria, diarrhea, and respiratory tract infection were also examined.

**METHODS**

**Setting**

Niger is a landlocked country of the Sahel with a population of approximately 14 million people. Household food production is linked to rainfed agriculture, in which staple crops such as millet and sorghum are harvested once per year from September to October. Each year, the decrease in food quantity and quality experienced in the months preceding the harvest (August to October) is associated with an increase in wasting among children younger than 5 years. Maradi, located in the south-central part of the country bordering Nigeria, has some of the highest rates of malnutrition in the country. The prevalence of wasting in Maradi was estimated to be 11.6% between January and May 2006.

Since 2001, Médecins Sans Frontières has provided treatment for severe wasting in Maradi at no cost in collaboration with the Ministry of Health of Niger. The therapeutic feeding program uses an outpatient approach to the treatment of malnutrition, through which children without serious complications are offered home-based treatment with the provision of RUTF. In 2006, treatment was extended to all children younger than 5 years and with moderate wasting (weight-for-height <80% of the NCHS reference median) with the aim of preventing the presentation of severe wasting.

**Study Design**

There are a total of 212 and 323 villages in the Maradi and Guidan Roumdji districts in the Maradi region, respectively. Villages eligible for inclusion in the study were those that had between 100 and 200 children aged 6 to 60 months according to the most recent Niger census, experienced a 15% or greater prevalence of wasting in 2005 according to admission records of local therapeutic feeding programs, were of Houssa ethnic majority (ie, fixed, not nomadic), and were not crossed by main (ie, paved) roads. Fourteen villages in Maradouna and 13 villages in Guidan Roumdji initially met the inclusion criteria, but 15 (8 in Maradouna and 7 in Guidan Roumdji) of these were removed after a field visit for verification. Therefore, a total of 12 villages (6 in each district) were identified that met the above criteria (Figure 1). The leaders of all 12 eligible villages were informed of the study objectives and protocol and agreed to participate.
The unit of randomization was the village, and intervention assignment was stratified by district and made through the random selection of village names from a hat. Selection was made by a member of the field team not involved in the identification of eligible villages. The first 3 villages drawn from the 6 eligible in a district were assigned to the intervention group. The remaining 3 villages in each district were assigned to the nonintervention group. Thus, a total of 6 villages were assigned to the intervention group and 6 villages to the nonintervention group. Assignment was not blinded due to the nature of the intervention.

Follow-up was conducted in the study villages on a monthly basis from August 2006 to March 2007. Children aged 6 to 60 months during the follow-up period were eligible for inclusion. Children younger than 6 months at the start of the study but reaching age 6 months during the follow-up period were recruited, while children reaching age 60 months were removed from follow-up.

Interventions
Children with weight-for-height 80% or more of the NCHS reference median in the 6 intervention villages received a monthly distribution of 1 sachet per day of RUTF (92 g [500 kcal/d]; Plumpy’nut; Nutriset, Malanay, France) from August to October 2006. Distributions of the preventive supplement were made by field teams of trained nutrition assistants and research nurses and took place at the same time as the study’s active surveillance activities. Children in the 6 nonintervention villages did not receive preventive supplementation.

During monthly follow-up visits, any child found with weight-for-height less than 80% of the NCHS reference median was referred to the neighboring government health facility. Treatment for malaria and uncomplicated diarrheal diseases was provided during the follow-up visit, if indicated.

Measurements
Surveillance activities, including anthropometric measurements and physical examinations, were conducted by field teams of trained nutrition assistants and research nurses in a dedicated central location in each village identified by the head of the village and field teams. Caregivers were asked to accompany their children to these sites for follow-up on a monthly basis. At the first visit, we administered a standardized questionnaire to obtain information on household, maternal, and child sociodemographic characteristics; child health history; and feeding practices. We estimated child age at recruitment using a special event calendar if exact date of birth was unknown. An abridged questionnaire was used at each follow-up visit to obtain information on major health events and feeding practices in the previous month.

At all visits, we measured child length/height and weight. Trained nutrition assistants carried out anthropometric measurements with the use of standardized methods and calibrated instruments. Child height (recumbent length if <85 cm) was measured to the nearest 0.1 cm using a wooden measurement board. Weight was measured to the nearest 0.1 kg using a hanging Salter scale.

The presence of malaria, respiratory tract infection, and diarrhea was determined by trained research nurses during the physical examinations and interviews with the mothers. A malaria HRP2 rapid diagnostic test (Paracheck-PF; Orchid Biomedical Laboratories, Goa, India) was used in children with fever to diagnose Plasmodium falciparum infection. Respiratory tract infection was defined as cough or difficulty breathing within the last 3 days, and diarrhea was defined as more than 3 loose stools within the last day, as reported by the mother. If a child did not present for a study visit in the village, the head of village provided the cause of absence. If a child had died, the cause of death was provided by a family member or the head of village.

When the proportion of children absent per village exceeded 5%, we scheduled additional study visits to facilitate complete measurements on all children. All the information was collected on standardized forms and double entered into a computer database (EpiData version 2.1; EpiData Association, Odense, Denmark).

Statistical Analyses
Our primary study outcome measures were individual WHZ score according to the World Health Organization Child Growth Standards and wasting (WHZ <-2). Our secondary measures included severe wasting (WHZ <-3), height-for-age z score (HAZ) according to the World Health Organization Child Growth Standards, stunting (HAZ <-2), severe stunting (HAZ <-3), mortality, and prevalence of malaria, diarrhea, and respiratory tract infection. To detect a difference of 50% in the incidence of wasting between groups with 90% power (at the 2-sided 5% level), accounting for a design effect of 2 owing to the cluster design and 15% loss to follow-up, we calculated that we would need to include 1000 children in each group. Analyses were by intention-to-treat. All children from villages initially assigned to the intervention group (or nonintervention group) were analyzed as from the intervention group (or nonintervention group).

To verify the randomization assumption, we compared the prevalence of baseline characteristics between intervention groups using generalized estimating equations to adjust standard errors for clustering at the village level.

We fitted mean WHZ and HAZ curves using mixed-effects models with restricted cubic splines. Knots were placed at 1, 2, 3, 4, and 5 months from the start of study. Covariates included...
the intervention group, linear and spline

terms for time (in months), and inter-
tion terms between intervention
group and time. We adjusted for child’s
age at recruitment, sex, baseline HAZ,
district, and interaction terms be-
tween these variables and time. Baseline
WHZ and its interaction with time
also were adjusted for when WHZ was
the dependent variable. Baseline WHZ
and HAZ were entered into the model
as continuous terms. The mixed-
effects models used hierarchal ran-
dom effects for the village, household,
and individual (intercept and slope for
linear time in the WHZ model) to ac-
count for the correlation at each level
when estimating the variance.15

All children with complete covariate
data, regardless of nutritional status, were
included in the longitudinal analyses of
WHZ and HAZ. The mixed-effects mod-
els do not require the same number of
observations on each child; therefore,
children with incomplete outcome data
were retained in the analysis. This re-
sulted in an “all available” analysis, in
which all available anthropometric mea-
surements on each child with complete
covariate data were included in the mod-
els. Observations with missing informa-
tion on any covariate in the adjusted
models were not included. Analyses that
carry forward the last value for missing
outcome data were conducted to assess
the sensitivity of these results to miss-
ing data. Weight-for-height z score was
not calculated for children with edema-
tous malnutrition. These observations
(n = 3) were therefore not included in
analyses of change in WHZ or the inci-
dence of wasting.

We estimated the intervention effect
from the spline model as the differ-
cence in attained WHZ and HAZ scores
between the intervention and nonin-
tervention groups every 2 months and
over the whole surveillance period. The
overall significance of the interven-
tion over the 8-month surveillance pe-
riod was assessed using a likelihood ra-
tio test comparing a model with main
effects for linear and nonlinear terms
for time against one with additional in-
teraction terms between intervention

effects for linear and nonlinear terms
for time.15 We used the likelihood ra-
tio test to assess whether intervention
effects were modified by child’s age at
recruitment by comparing a main-
effects model against one with addi-
tional interaction terms between inter-
vention group, time, and age. In
supplemental analyses, we stratified by
child’s age at recruitment.

We examined treatment effects on the
incidence of wasting and stunting among
children free from the outcome at re-
cruitment. Mortality events included all
reports for which the cause for absence
from study visits was reported to be death
by a family member or the head of vil-
lage. Children contributed person-time
to the analysis from recruitment until the
first occurrence of the outcome, the end
of eligibility when age exceeded 60
months, or the end of study in March
2007. Incidence rates by village were es-
timated as the number of observed events
over the number of child-months con-
tributed to follow-up. Incidence rates by
intervention group were estimated by
taking the mean of the corresponding vil-
lage incidence rates, weighted by the
number of child-months from each vil-
lage that contributed to the mean.16 We
calculated incidence rate ratios by divid-
ing the weighted mean from the inter-
vention group by the weighted mean from
the nonintervention group. Con-
fidence intervals (CIs) around the rate
ratios were estimated using the Taylor
Series approximations to obtain stan-
dard errors.17

Next we estimated adjusted hazard
ratios from a marginal Cox propor-
tional hazards model with time from
recruitment to the event (wasting,
stunting, or death) as the outcome and
calendar month as the time scale. We
adjusted for child’s age at recruit-
ment, sex, baseline HAZ, and district.
Baseline WHZ was adjusted for when
wasting was the dependent variable.
Confidence intervals used robust esti-
mates of the variance to account for
clustering at the village level.

We calculated the prevalence of ma-
laria, respiratory tract infection, and di-
arrhea by village as the number of vis-
its with a positive diagnosis divided by
the total number of visits. Prevalence
by intervention group was calculated
by taking the mean of the correspond-
ing village prevalences, weighted by the
child-months of observation from each
village. Confidence intervals around the
prevalence ratios were estimated using
the Taylor series approximations to ob-
tain standard errors.17 We estimated ad-
justed odds ratios from generalized lin-
er mixed-effects models with presence
of the morbidity as the outcome and
predictors that included intervention
group, child’s age at recruitment, sex,
baseline HAZ, district, and calendar
month. Confidence intervals were ad-
justed for clustering at the village,
household, and individual levels using
random effects. We used the Wald test
to assess whether intervention effects
on morbidity were modified by child’s
age at recruitment. In the analysis of all
binary outcomes, observations with
missing outcome data were assumed to
represent the nonoccurrence of an
event. To assess the sensitivity of the
results to missing data, additional analy-
ses were conducted that either as-
sumed an event occurred or censored
the observation when the outcome data
were missing.

P ≤ .05 was considered statistically
significant. No adjustments were made
for multiple comparisons. Analyses were
conducted using SAS version 9.1
(SAS Institute Inc, Cary, North Caro-
olina) and MLwiN 2.0 (Institute of Edu-
cation, London, United Kingdom).

Ethics
The study protocol was approved by the
Comité de Protection des Personnes,
“Ile-de-France XI,” France, and the
Ministry of Health of Niger. The Har-
vard School of Public Health granted an
exemption for the Harvard investiga-
tor to conduct the data analyses with
the previously collected data. Ap-
proval from all heads of villages was re-
ceived prior to the start of the study.
The objectives of the study and the
study protocol were explained to heads
of households with children aged 6 to
60 months before inclusion. An in-
formed consent statement was read aloud in the local dialect before being signed or fingerprinted by the head of household or child caregiver.

RESULTS
The overall sample size was 3533 children, corresponding to 1407 households. Forty-five percent of children (n=1592) were between 6 and 24 months of age at recruitment. Mean maternal age was 26.6 (SD, 6.7) years, and educational attainment among mothers was low, with only 3% ever attending school. Sociodemographic characteristics of children at recruitment, including age, sex, ethnicity, maternal age and maternal education, and prevalence of wasting at recruitment, did not differ by intervention group (Table 1). Children in the nonintervention group were more likely to be stunted. During the 8-month surveillance period, there was a median of 8 visits per child (mean, 6.9 [SD, 2.0]). The number of children with height and weight measurements in August, October, December, and February was 1477, 1475, 1391, and 1452, respectively, in the intervention group and 1689, 1635, 1545, and 1574 in the nonintervention group. Children contributed a total of 25,012 months to follow-up for the survival end point. Follow-up was similar by intervention group (95% CI, −0.23 to 0.03) at baseline and 0.02 to 0.20 at the end of follow-up. The effect of the intervention on HAZ change from baseline to the end of follow-up was thus 0.14 (95% CI, 0.11 to 0.18). The difference in HAZ change between the intervention and nonintervention groups was 0.06 (95% CI, −0.04 to 0.16) in October, 0.09 (95% CI, −0.01 to 0.19) in December, and 0.08 (95% CI, −0.02 to 0.18) in February (Figure 2). Results for differences in WHZ and HAZ did not appreciably change with the last value carried forward for missing outcome data.

Among children without each of these outcomes at recruitment, the absolute rate of wasting and severe wasting, respectively, was 0.17 events per child-year (140 wasting events/841 child-years) and 0.03 events per child-year (29 severe wasting events/943 child-years).

### Table 1. Participant Characteristics at Recruitment by Intervention Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention</th>
<th>Nonintervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of villages</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>No. of children</td>
<td>1671</td>
<td>1862</td>
</tr>
<tr>
<td>Person-time, mo</td>
<td>11 830</td>
<td>13 182</td>
</tr>
</tbody>
</table>

Child characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention</th>
<th>Nonintervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child age at recruitment, mean (SD), mo</td>
<td>30.0 (16.9)</td>
<td>29.0 (16.3)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Mean</td>
<td>857 (51.3)</td>
<td>926 (49.8)</td>
</tr>
<tr>
<td>Female</td>
<td>813 (48.7)</td>
<td>935 (50.2)</td>
</tr>
<tr>
<td>Wasting at recruitment</td>
<td>WHZ, mean (SD)</td>
<td>−0.7 (1.0)</td>
</tr>
<tr>
<td>Wasting (WHZ &lt; -2)</td>
<td>137 (8.2)</td>
<td>159 (8.6)</td>
</tr>
<tr>
<td>Severe wasting (WHZ &lt; -3)</td>
<td>17 (1.0)</td>
<td>25 (1.4)</td>
</tr>
<tr>
<td>Stunting at recruitment</td>
<td>HAZ, mean (SD)</td>
<td>−1.9 (1.3)</td>
</tr>
<tr>
<td>Stunting (HAZ &lt; -2)</td>
<td>777 (46.7)</td>
<td>1046 (56.2)</td>
</tr>
<tr>
<td>Severe stunting (HAZ &lt; -3)</td>
<td>293 (17.6)</td>
<td>519 (27.9)</td>
</tr>
<tr>
<td>Breastfed &lt; 6 mo</td>
<td>577 (35.1)</td>
<td>622 (34.0)</td>
</tr>
<tr>
<td>Hospitalized during last mo</td>
<td>69 (4.2)</td>
<td>167 (9.3)</td>
</tr>
<tr>
<td>Malaria diagnosis at recruitment</td>
<td>20 (1.3)</td>
<td>56 (3.1)</td>
</tr>
</tbody>
</table>

Maternal characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention</th>
<th>Nonintervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>13-19</td>
<td>20-29</td>
</tr>
<tr>
<td>176 (11.6)</td>
<td>880 (58.0)</td>
<td>462 (30.4)</td>
</tr>
<tr>
<td>Ever attended school</td>
<td>49 (3.0)</td>
<td>63 (3.5)</td>
</tr>
<tr>
<td>No. of co-wives</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>11 (0.7)</td>
<td>616 (38.0)</td>
<td>866 (53.5)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>21.8 (7.1)</td>
<td>21.1 (4.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention</th>
<th>Nonintervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of children &lt; 5 y at home</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>169 (10.5)</td>
<td>192 (10.6)</td>
<td></td>
</tr>
<tr>
<td>469 (29.0)</td>
<td>585 (32.3)</td>
<td></td>
</tr>
<tr>
<td>386 (23.9)</td>
<td>460 (25.4)</td>
<td></td>
</tr>
<tr>
<td>591 (36.6)</td>
<td>573 (31.7)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HAZ, height-for-age z score; WHZ, weight-for-height z score.

aIntervention groups were not significantly different from each other with the exception of a higher prevalence of stunting (P=.007) and severe stunting (P=.007) at recruitment in the nonintervention group compared with the intervention group.

bDetermined by rapid fingerstick assay.

cCalculated as weight in kilograms divided by height in meters squared.
child-years) in the intervention group, as compared with 0.26 events per child-year (233 wasting events/895 child-years) and 0.07 events per child-year (71 severe wasting events/1029 child-years) in the nonintervention group. The intervention thus resulted in a 36% (95% CI, 17% to 50%; \(P<.001\)) reduction in the incidence of wasting and a 58% (95% CI, 43% to 68%; \(P<.001\)) reduction in the incidence of severe wasting (TABLE 2). These effects were not modified by age at recruitment.

There were no significant effects on the prevalence of malaria, diarrhea, or respiratory tract infection (TABLE 3).

## COMMENT

This cluster randomized trial examined the effect of short-term, preventive supplementation with RUTF on the nutritional status, mortality, and morbidity of children aged 6 to 60 months. We found a protective effect of the intervention on WHZ change and a significant reduction in the incidence of wasting and severe wasting.

To our knowledge, this is the first population-based study to evaluate the effectiveness of RUTF in the prevention of wasting, but the protective effect of this intervention on WHZ decline and wasting incidence is consistent with the therapeutic use of RUTF in a variety of settings.\(^6,8,9,18\) Ready-to-use therapeutic food has been shown to increase energy and micronutrient intake in children younger than 5 years.\(^6,18\) The increase in energy intake associated with RUTF supplementation likely contributes to weight gain. The possibility of weight gain due to improved appetite from increased micronutrient intake has been suggested by others\(^19\) but has not been consistent.\(^20\)

This study found a mean adjusted difference in WHZ of 0.22 \(z\) between the intervention and nonintervention groups from baseline to the end of follow-up. An increase of this magnitude in the mean WHZ score can reduce the population prevalence of wasting and severe wasting. At the individual level, because a child’s risk of death increases exponentially with decreasing nutritional status,\(^21\) the clinical importance of the observed intervention effect to prevent a decrease in WHZ score is expected to be greatest among children with lower WHZ scores and higher risks of death.

Sample sizes were not calculated to estimate differences in groups between the periods during and after supplementation. However, the data suggest that the intervention effect on WHZ change was greatest during the 3-month period that coincided with the actual administration of the supplement and a period of acute food inse-
curency preceding the harvest. Only a small benefit of supplementation appears to be sustained in the months after supplementation ceased. This suggests that short-term supplementation with RUTF may be targeted to suitably address specific, short-term nutrition needs, but further study is required to assess possible long-term improvements.

We found a limited effect of RUTF supplementation on HAZ, but the magnitude of difference in HAZ is in the range reported in trials assessing the effectiveness of complementary feeding practices in older infants. The small effect on HAZ change found here is likely due to the short duration of supplementation. The 3-month intervention may have been too short to demonstrate an important effect on linear growth. A recent review of complementary feeding interventions suggests that the effect of similar programs on linear growth has been inconsistent, with significant improvements achieved in only some settings.

Twenty-five children died during the study period. While the difference between the groups was not statistically significant, less than half as many deaths occurred in the intervention group than in the nonintervention group. A study from Malawi on the effectiveness of home-based treatment with RUTF found a similar nonsignificant decrease in mortality risk associated with RUTF supplementation compared to standard therapy. Data on the reported cause of death in this study suggest differences in malnutrition (2/18 deaths in the nonintervention group vs 0/7 in the intervention group) and malaria (7/18 deaths in the nonintervention group vs 2/7 in the intervention group). Cause of death, however, was determined by verbal autopsy, which is not well-suited to distinguishing between causes of deaths with similar features and may suffer from misclassification. Interpretation of these data will therefore require caution.

There was no evidence of increased risk of malaria associated with RUTF supplementation. Findings of adverse health effects due to iron and folic acid supplementation in a large community-based randomized controlled trial in Zanzibar have suggested that iron supplementation should proceed cautiously in settings where the prevalence of malaria and other infectious diseases is high. This study, however, suggests that RUTF, which is fortified with iron (11.5 g/100 g) and other micronutrients, is unlikely to increase the prevalence of malaria. Further research is warranted to examine the effect of RUTF on the incidence of malaria.

The association of undernutrition and increased susceptibility to infectious disease is well known, and evidence is accumulating on the possible protective effect of some micronutrients, such as zinc, on diarrhea and respiratory tract infection. The lack of a significant effect on diarrhea and respiratory tract infection in this study may be owing to the nonspecific nature of the diagnoses based on maternal report, the competing absorption of multiple micronutrients such as zinc and iron, or insufficient dosages of these micronutrients in RUTF. Two studies have previously reported on the effect of RUTF on morbidity, but results have been inconsistent.

Our study has several limitations. First, the small number of clusters may have limited the benefits of randomization, resulting in unmeasured confounding. Intervention groups did not significantly differ from each other for child, maternal, and household characteristics, with the exception of a higher prevalence of stunting at recruitment in the nonintervention group. Imbalances in height-for-age were accounted for in all multivariate regression models.

### Table 2. Effect of Ready-to-Use Therapeutic Food Supplementation on Wasting and Stunting

<table>
<thead>
<tr>
<th>Measure</th>
<th>Intervention</th>
<th>Nonintervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of children</td>
<td>1534</td>
<td>1702</td>
</tr>
<tr>
<td>No. of events/No. of child-years</td>
<td>140/841</td>
<td>233/895</td>
</tr>
<tr>
<td>Incidence rate per child-year (95% CI)</td>
<td>0.17 (0.13-0.21)</td>
<td>0.26 (0.21-0.33)</td>
</tr>
<tr>
<td>Incidence rate ratio (95% CI)</td>
<td>0.64 (0.52-0.79)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>0.64 (0.50-0.83)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Severe wasting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of children</td>
<td>1654</td>
<td>1836</td>
</tr>
<tr>
<td>No. of events/No. of child-years</td>
<td>29/943</td>
<td>71/1029</td>
</tr>
<tr>
<td>Incidence rate per child-year (95% CI)</td>
<td>0.03 (0.02-0.04)</td>
<td>0.07 (0.05-0.09)</td>
</tr>
<tr>
<td>Incidence rate ratio (95% CI)</td>
<td>0.45 (0.29-0.69)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>0.42 (0.32-0.57)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Stunting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of children</td>
<td>894</td>
<td>816</td>
</tr>
<tr>
<td>No. of events/No. of child-years</td>
<td>134/453</td>
<td>163/391</td>
</tr>
<tr>
<td>Incidence rate per child-year (95% CI)</td>
<td>0.30 (0.23-0.38)</td>
<td>0.42 (0.30-0.57)</td>
</tr>
<tr>
<td>Incidence rate ratio (95% CI)</td>
<td>0.71 (0.57-0.89)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>0.75 (0.54-1.04)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Severe stunting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of children</td>
<td>1378</td>
<td>1343</td>
</tr>
<tr>
<td>No. of events/No. of child-years</td>
<td>1117/749</td>
<td>144/702</td>
</tr>
<tr>
<td>Incidence rate per child-year (95% CI)</td>
<td>0.15 (0.11-0.20)</td>
<td>0.21 (0.18-0.24)</td>
</tr>
<tr>
<td>Incidence rate ratio (95% CI)</td>
<td>0.72 (0.56-0.93)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>0.80 (0.58-1.10)</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

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eration of the effect of differences in other specific baseline characteristics, including the frequency of hospitalization in the previous month and the prevalence of malaria, was also made. Because of their low prevalence, these factors were unlikely to strongly confound, or explain away, the observed differences attributed to the intervention. In multivariate regression models, the inclusion of these variables did not appreciably affect results. Potential measurement error of child’s age at recruitment and of anthropometric variables, such as height/length, may have resulted in residual confounding and reduced the statistical power to detect significant effects, respectively.

This study was unblinded with respect to intervention assignment; however, we do not expect this to have had a differential effect on standardized anthropometric measurements. It did not appear to affect follow-up. This study also was not able to collect complete response data on all children, introducing the potential for bias if the mechanism for missing data cannot be ignored. The proportion of missing data, however, is relatively small at each point during follow-up, and sensitivity analyses were used to assess the potential effect of missing response. Different strategies to account for the missing data did not appreciably change our conclusions.

We were unable to measure dietary intakes at recruitment or during the intervention. We therefore did not have information on average energy intake, the macronutrient and micronutrient composition of baseline diets, or the energy received from the supplement vs household foods during the intervention to indicate whether RUTF supplemented or displaced usual intake. Adherence was similarly not measured, limiting our understanding of how the supplement was used by each child and within the household.

The likelihood of contamination was reduced using village- rather than individual-level randomization. Contamination between intervention and nonintervention villages is also unlikely, owing to their geographic separation. There was no evidence of resale of the supplement in local markets to suggest that individuals from nonintervention villages would have been able to access the study supplement outside the study. No secular changes were observed in the health and nutritional status of children in the study villages during the 8 months of follow-up.

These results are applicable to other settings of acute food insecurity, where access to food is limited due to emergency or seasonal conditions and where short-term food supplementation is required for the prevention of wasting. The effectiveness of preventive supplementation with RUTF in other settings may depend on RUTF acceptability, the extent of resale after distribution, and the adequacy of the public health and nutrition systems in place. Further research is warranted to identify the minimal dose required to achieve an effect and to compare the effect of other formulations of RUTF and locally available diets, which also may be effective in improving nutritional status in children.\textsuperscript{29,30} Information is also needed on the cost-effectiveness and feasibility of large-scale RUTF distribution. The relatively high costs of imported RUTF (US $4.54/kg before duties and shipping [Guillaume Sauvage, Médecins Sans Frontières, Paris, France, written communication, July 2008]) and locally produced RUTF (US $3.66/kg before duties [Mark Manary, Department of Pediatrics, Washington University)

### Table 3. Effect of Ready-to-Use Therapeutic Food Supplementation on Mortality and Morbidity

<table>
<thead>
<tr>
<th>Measure</th>
<th>Intervention</th>
<th>Nonintervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of children\textsuperscript{a}</td>
<td>1671</td>
<td>1862</td>
</tr>
<tr>
<td>No. of events/No. of child-years</td>
<td>7,986</td>
<td>19,1099</td>
</tr>
<tr>
<td>Incidence rate per child-year (95% CI)\textsuperscript{b}</td>
<td>0.007 (0.003-0.015)</td>
<td>0.016 (0.011-0.026)</td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>0.43 (0.18-1.04)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)\textsuperscript{c}</td>
<td>0.51 (0.25-1.05)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td><strong>Malaria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of children\textsuperscript{a}</td>
<td>1671</td>
<td>1862</td>
</tr>
<tr>
<td>No. of visits with diagnosis/total No. of visits</td>
<td>330/11,542</td>
<td>721/12,789</td>
</tr>
<tr>
<td>Prevalence, % (95% CI)\textsuperscript{d}</td>
<td>2.86 (0.78-4.94)</td>
<td>5.64 (1.53-9.74)</td>
</tr>
<tr>
<td>Prevalence ratio (95% CI)</td>
<td>0.51 (0.45-0.58)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)\textsuperscript{e}</td>
<td>0.76 (0.51-1.13)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of children\textsuperscript{a}</td>
<td>1671</td>
<td>1862</td>
</tr>
<tr>
<td>No. of visits with diagnosis/total No. of visits</td>
<td>156/11,542</td>
<td>170/12,789</td>
</tr>
<tr>
<td>Prevalence, % (95% CI)\textsuperscript{d}</td>
<td>1.35 (0.74-1.96)</td>
<td>1.33 (1.03-1.63)</td>
</tr>
<tr>
<td>Prevalence ratio (95% CI)</td>
<td>1.02 (0.82-1.26)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)\textsuperscript{e}</td>
<td>1.07 (0.88-1.28)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td><strong>Respiratory tract infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of children\textsuperscript{a}</td>
<td>1671</td>
<td>1862</td>
</tr>
<tr>
<td>No. of visits with diagnosis/total No. of visits</td>
<td>117/11,542</td>
<td>114/12,789</td>
</tr>
<tr>
<td>Prevalence, % (95% CI)\textsuperscript{d}</td>
<td>1.01 (0.44-1.59)</td>
<td>0.89 (0.37-1.41)</td>
</tr>
<tr>
<td>Prevalence ratio (95% CI)</td>
<td>1.14 (0.88-1.47)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)\textsuperscript{e}</td>
<td>1.21 (0.89-1.63)</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio.
\textsuperscript{a}Contributing to the crude analysis.
\textsuperscript{b}Incidence rates by intervention group were estimated by taking the mean of the corresponding village incidence rates, weighted by the person-months of observation from each village that contributed to the mean.
\textsuperscript{c}Adjusted HRs were estimated from a marginal Cox proportional hazards model with time from recruitment to the event as the outcome and predictors that included intervention group, child age at recruitment, sex, baseline height-for-age z score, district, and calendar month.
\textsuperscript{d}Prevalence was calculated by summing the number of visits the child had the morbidity diagnosis divided by the number of visits. Mean prevalence was calculated by taking the mean of the village prevalence weighted by the person-months of observation from each village.
\textsuperscript{e}Adjusted ORs were estimated from generalized linear mixed-effects models with presence of the morbidity as the outcome and predictors that included intervention group, child age at recruitment, sex, baseline height-for-age z score, district, and calendar month.
School of Medicine, St Louis, Missouri, written communication, July 2008) may challenge the effective scaling up of short-term experiences such as these.

In conclusion, this study demonstrates that the distribution of RUTF to nonmalnourished children aged 6 to 60 months can be effective in limiting reductions in WHZ and reducing the incidence of wasting and severe wasting in the short term. The effectiveness of any intervention to prevent malnutrition, however, will ultimately depend on its consideration of the underlying causes of malnutrition, integration with other broad-based strategies to improve public nutrition, and feasibility within the resource constraints of humanitarian and public health programming.

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Author Contributions: Ms Isanaka had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of the data: Isanaka, Nombela, Djibo, Guerin, Grais.

Drafting of the manuscript: Isanaka.

Critical revision of the manuscript for important intellectual content: Isanaka, Nombela, Djibo, Poupard, Van Beckhoven, Gaboulov, Guerin, Grais.

Statistical analysis: Isanaka, Grais.

Obtained funding: Guerin, Grais.

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Role of the Sponsor: MSF reviewed the final study protocol but had no role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data; or the preparation of the manuscript.

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