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*JAMA*. 2009;301(3):277-285 (doi:10.1001/jama.2008.1018)

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# 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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**W**ASTING (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<sup>1</sup> and is an important contributor to the population-attributable risk of child mortality and overall burden of disease.<sup>2</sup> New outpatient and community-based models for the treatment of wasting have been shown effective in the rehabilitation of children with severe wasting.<sup>3,4</sup> 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.<sup>5,6</sup>

Ready-to-use therapeutic food has been shown effective in the treatment of severe and moderate wasting<sup>6-8</sup> and was associated with higher recovery and

**Context** Ready-to-use therapeutic foods (RUTFs) are an important component of effective outpatient treatment of severe wasting. 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  $-0.10 z$  (95% confidence interval [CI],  $-0.23$  to  $0.03$ ) at baseline and  $0.12 z$  (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  $0.22 z$  (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.

**Trial Registration** clinicaltrials.gov Identifier: NCT00682708

JAMA. 2009;301(3):277-285

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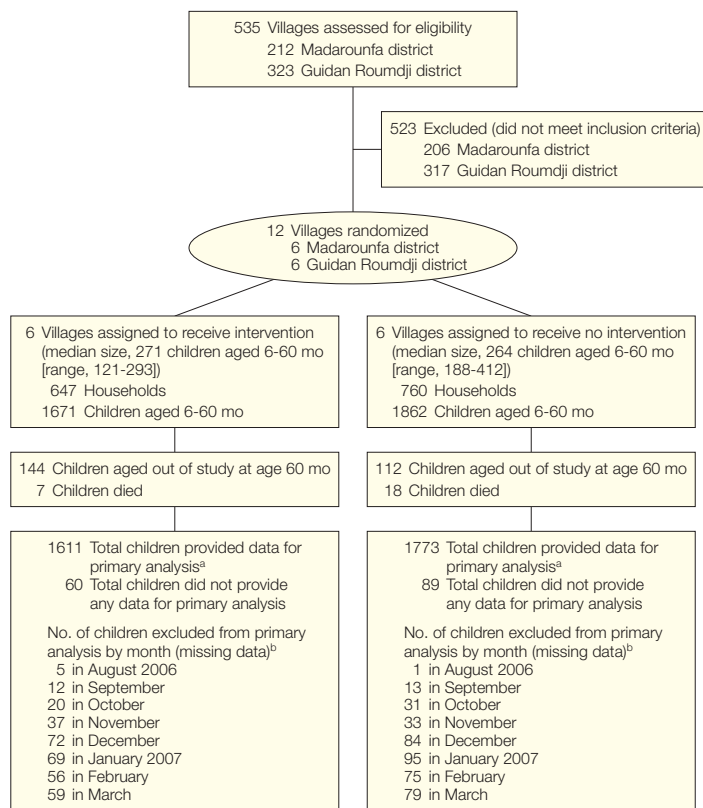
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**For editorial comment see p 327.**

**Figure 1.** Intervention Assignment and Completed Follow-up



<sup>a</sup>See Figure 2 for numbers of children providing data by month.  
<sup>b</sup>Includes 60 (intervention) and 89 (nonintervention) children who did not provide any data for primary analysis.

rates of weight gain among children at nutritional risk presenting to health centers in Malawi.<sup>9</sup> 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 pre-

ceding 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.<sup>10</sup> Household food production is linked to rain-fed 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.<sup>11</sup> The prevalence of wasting in Maradi was estimated to be 11.6% between January and May 2006.<sup>11</sup>

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 Madarounfa and Guidan Rourdji 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,<sup>12</sup> 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 Madarounfa and 13 villages in Guidan Rourdji initially met the inclusion criteria, but 15 (8 in Madarounfa and 7 in Guidan Rourdji) 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, Malau-nay, 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 noninter-vention 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 nutritional programs or health centers in the area for treatment provided at no cost. Outpatient treatment in the local nutritional programs consisted of 2 sachets per day of RUTF and weekly follow-up. Inpatient care was made available to chil-

dren who presented with medical complications. Other medical conditions identified during follow-up were referred to the neighboring governmental health facility. Treatment for malaria and noncomplicated 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<sup>13</sup> 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.<sup>14</sup> 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 interaction terms between intervention group and time. We adjusted for child's age at recruitment, sex, baseline HAZ, district, and interaction terms between 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 hierarchical random effects for the village, household, and individual (intercept and slope for linear time in the WHZ model) to account for the correlation at each level when estimating the variance.<sup>15</sup>

All children with complete covariate data, regardless of nutritional status, were included in the longitudinal analyses of WHZ and HAZ. The mixed-effects models do not require the same number of observations on each child; therefore, children with incomplete outcome data were retained in the analysis. This resulted in an "all available" analysis, in which all available anthropometric measurements on each child with complete covariate data were included in the models. Observations with missing information 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 missing data. Weight-for-height *z* score was not calculated for children with edematous malnutrition. These observations (*n*=3) were therefore not included in analyses of change in WHZ or the incidence of wasting.

We estimated the intervention effect from the spline model as the difference in attained WHZ and HAZ scores between the intervention and nonintervention groups every 2 months and over the whole surveillance period. The overall significance of the intervention over the 8-month surveillance period was assessed using a likelihood ratio test comparing a model with main effects for linear and nonlinear terms for time against one with additional interaction terms between intervention

group and linear and nonlinear terms for time.<sup>15</sup> We used the likelihood ratio test to assess whether intervention effects were modified by child's age at recruitment by comparing a main-effects model against one with additional interaction terms between intervention 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 recruitment. 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 village. 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 estimated as the number of observed events over the number of child-months contributed to follow-up. Incidence rates by intervention group were estimated by taking the mean of the corresponding village incidence rates, weighted by the number of child-months from each village that contributed to the mean.<sup>16</sup> We calculated incidence rate ratios by dividing the weighted mean from the intervention group by the weighted mean from the nonintervention group. Confidence intervals (CIs) around the rate ratios were estimated using the Taylor Series approximations to obtain standard errors.<sup>17</sup>

Next we estimated adjusted hazard ratios from a marginal Cox proportional 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 recruitment, sex, baseline HAZ, and district. Baseline WHZ was adjusted for when wasting was the dependent variable. Confidence intervals used robust estimates of the variance to account for clustering at the village level.

We calculated the prevalence of malaria, respiratory tract infection, and diarrhea 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 corresponding 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 obtain standard errors.<sup>17</sup> We estimated adjusted odds ratios from generalized linear 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 adjusted 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 analyses were conducted that either assumed 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 Carolina) and MLwiN 2.0 (Institute of Education, 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 Harvard School of Public Health granted an exemption for the Harvard investigator to conduct the data analyses with the previously collected data. Approval from all heads of villages was received 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 in the 2 groups.

We found a significant difference in the rate of change in WHZ by intervention group over the 8-month surveillance period (P < .001). The WHZ differences in the intervention and nonintervention groups at baseline and at the end of follow-up were -0.10 z (95% CI, -0.23 to 0.03) and 0.12 z (95% CI, 0.02 to 0.21), respectively; thus, the overall effect of the intervention on WHZ change over 8 months was 0.22 z (95% CI, 0.13 to 0.30). Mean adjusted WHZ differences between the intervention and nonintervention groups were 0.21 z (95% CI, 0.12 to 0.29) in October, 0.09 z (95% CI, 0.01 to 0.18) in December, and 0.11 z (95% CI, 0.02 to 0.20) in February (FIGURE 2). There was no significant interaction by child age at baseline (P = .07 for interaction). The intraclass correlation coefficient was 0.015.

The overall rate of HAZ change differed by intervention group over the

8-month surveillance period (P < .001). The HAZ difference in the intervention and nonintervention groups was -0.06 z (95% CI, -0.18 to 0.06) at baseline and 0.08 z (95% CI, -0.02 to 0.18) 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 z (95% CI, 0.11 to 0.18). The difference in HAZ change between the intervention and nonintervention groups was 0.06 z (95% CI, -0.04 to 0.16) in October, 0.09 z (95% CI, -0.01

to 0.19) in December, and 0.08 z (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

**Table 1.** Participant Characteristics at Recruitment by Intervention Group<sup>a</sup>

Characteristic	No. (%)	
	Intervention	Nonintervention
No. of villages	6	6
No. of children	1671	1862
Person-time, mo	11 830	13 182
Child characteristics		
Child age at recruitment, mean (SD), mo	30.0 (16.9)	29.0 (16.3)
Sex		
Male	857 (51.3)	926 (49.8)
Female	813 (48.7)	935 (50.2)
Wasting at recruitment		
WHZ, mean (SD)	-0.7 (1.0)	-0.7 (1.0)
Wasting (WHZ < -2)	137 (8.2)	159 (8.6)
Severe wasting (WHZ < -3)	17 (1.0)	25 (1.4)
Stunting at recruitment		
HAZ, mean (SD)	-1.9 (1.3)	-2.2 (1.3)
Stunting (HAZ < -2)	777 (46.7)	1046 (56.2)
Severe stunting (HAZ < -3)	293 (17.6)	519 (27.9)
Breastfed <6 mo	577 (35.1)	622 (34.0)
Hospitalized during last mo	69 (4.2)	167 (9.3)
Malaria diagnosis at recruitment <sup>b</sup>	20 (1.3)	56 (3.1)
Maternal characteristics		
Age, y		
13-19	176 (11.6)	168 (9.6)
20-29	880 (58.0)	1040 (59.5)
≥30	462 (30.4)	539 (30.9)
Ever attended school	49 (3.0)	63 (3.5)
No. of co-wives		
0	11 (0.7)	1 (0.1)
1	616 (38.0)	777 (42.8)
2	866 (53.5)	874 (48.1)
≥3	127 (7.8)	164 (9.0)
Body mass index, mean (SD) <sup>c</sup>	21.8 (7.1)	21.1 (4.2)
No. of children <5 y at home		
1	169 (10.5)	192 (10.6)
2	469 (29.0)	585 (32.3)
3	386 (23.9)	460 (25.4)
≥4	591 (36.6)	573 (31.7)

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

<sup>a</sup>Intervention groups were not significantly different from each other with the exception of a higher prevalence of stunting (P = .05) and severe stunting (P = .007) at recruitment in the nonintervention group compared with the intervention group.

<sup>b</sup>Determined by rapid fingerstick assay.

<sup>c</sup>Calculated 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 incidence of stunting. These results did not change under alternative assumptions for missing data.

The mortality rate did not differ between groups, with 0.007 deaths per child-year (7 deaths/986 child-years) in the intervention group and 0.016 deaths per child-year (16 deaths/1099 child-years) in the nonintervention group (adjusted hazard ratio, 0.51; 95% CI, 0.25 to 1.05) (TABLE 3). We observed no effect of the intervention on the

prevalence of malaria, diarrhea, or respiratory tract infection (Table 3).

**COMMENT**

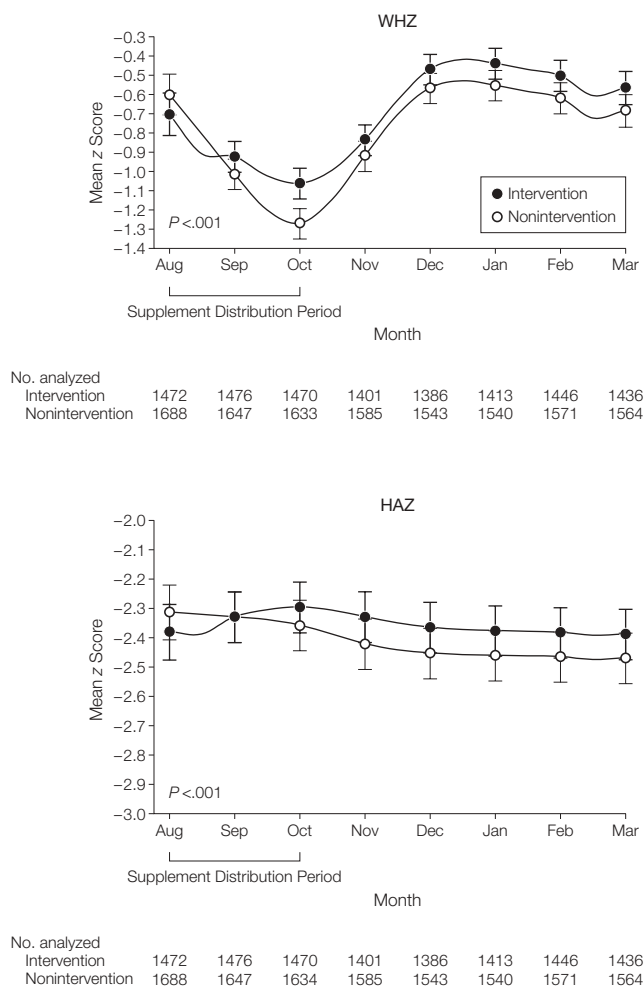
This cluster randomized trial examined the effect of short-term, preventive supplementation with RUTF on the nutritional status, mortality, and morbidity of children aged 6 to 60 months. We found a protective effect of the intervention on WHZ change and a significant reduction in the incidence of wasting 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.<sup>3,6,8,9,18</sup> Ready-to-use therapeutic food has been shown to increase energy and micronutrient intake in children younger than 5 years.<sup>6,18</sup> 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<sup>19</sup> but has not been consistent.<sup>20</sup>

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,<sup>21</sup> 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-

**Figure 2.** Weight-for-Height z Scores (WHZs) and Height-for-Age z Scores (HAZs) Over the 8-Month Surveillance Period (August 2006-March 2007)



Plotted values were estimated from adjusted cubic spline models and represent the mean values for a male child in Madarounfa district with mean baseline WHZ score and mean baseline HAZ score at age 18 months at recruitment. Because the model includes no interactions with the intervention group, the shape and differences between curves at each point shown are representative of the entire study population.  $P$  values were derived from a likelihood ratio test comparing a model with main effects for linear and nonlinear terms for time against one with additional interaction terms between intervention group and linear and nonlinear terms for time. Error bars indicate 95% confidence intervals.

curity 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.<sup>22</sup> 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.<sup>23</sup>

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.<sup>3</sup> 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.<sup>24</sup> 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.<sup>25</sup> 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,<sup>26</sup> and evidence is accumulating on the possible protective effect of some micronutrients, such as zinc, on diarrhea and respiratory tract infection.<sup>27,28</sup> The lack of a significant effect on diarrhea and res-

piratory 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.<sup>3,18</sup>

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. Consid-

**Table 2.** Effect of Ready-to-Use Therapeutic Food Supplementation on Wasting and Stunting<sup>a</sup>

Measure	Intervention	Nonintervention
<b>Wasting</b>		
No. of children <sup>b</sup>	1534	1702
No. of events/No. of child-years	140/841	233/895
Incidence rate per child-year (95% CI) <sup>c</sup>	0.17 (0.13-0.21)	0.26 (0.21-0.33)
Incidence rate ratio (95% CI)	0.64 (0.52-0.79)	1 [Reference]
Adjusted HR (95% CI) <sup>d</sup>	0.64 (0.50-0.83)	1 [Reference]
<b>Severe wasting</b>		
No. of children <sup>b</sup>	1654	1836
No. of events/No. of child-years	29/943	71/1029
Incidence rate per child-year (95% CI) <sup>c</sup>	0.03 (0.02-0.04)	0.07 (0.05-0.09)
Incidence rate ratio (95% CI)	0.45 (0.29-0.69)	1 [Reference]
Adjusted HR (95% CI) <sup>d</sup>	0.42 (0.32-0.57)	1 [Reference]
<b>Stunting</b>		
No. of children <sup>b</sup>	894	816
No. of events/No. of child-years	134/453	163/391
Incidence rate per child-year (95% CI) <sup>c</sup>	0.30 (0.23-0.38)	0.42 (0.30-0.57)
Incidence rate ratio (95% CI)	0.71 (0.57-0.89)	1 [Reference]
Adjusted HR (95% CI) <sup>d</sup>	0.75 (0.54-1.04)	1 [Reference]
<b>Severe stunting</b>		
No. of children <sup>b</sup>	1378	1343
No. of events/No. of child-years	111/749	144/702
Incidence rate per child-year (95% CI) <sup>c</sup>	0.15 (0.11-0.20)	0.21 (0.18-0.24)
Incidence rate ratio (95% CI)	0.72 (0.56-0.93)	1 [Reference]
Adjusted HR (95% CI) <sup>d</sup>	0.80 (0.58-1.10)	1 [Reference]

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

<sup>a</sup> Analysis includes only those children free of the outcome at recruitment. Wasting and severe wasting are defined as weight-for-height z score (WHZ) less than -2 and WHZ less than -3, respectively. Stunting and severe stunting are defined as height-for-age z score (HAZ) less than -2 and HAZ less than -3, respectively.

<sup>b</sup> Contributing to the crude analysis.

<sup>c</sup> 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.

<sup>d</sup> 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 HAZ, and district. Baseline WHZ also was adjusted for when wasting was the dependent variable.

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; how-

ever, 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 non-intervention 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.<sup>29,30</sup> 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

Measure	Intervention	Nonintervention
<b>Mortality</b>		
No. of children <sup>a</sup>	1671	1862
No. of events/No. of child-years	7/986	18/1099
Incidence rate per child-year (95% CI) <sup>b</sup>	0.007 (0.003-0.015)	0.016 (0.011-0.026)
Incidence rate ratio (95% CI)	0.43 (0.18-1.04)	1 [Reference]
Adjusted HR (95% CI) <sup>c</sup>	0.51 (0.25-1.05)	1 [Reference]
<b>Malaria</b>		
No. of children <sup>a</sup>	1671	1862
No. of visits with diagnosis/total No. of visits	330/11 542	721/12 789
Prevalence, % (95% CI) <sup>d</sup>	2.86 (0.78-4.94)	5.64 (1.53-9.74)
Prevalence ratio (95% CI)	0.51 (0.45-0.58)	1 [Reference]
Adjusted OR (95% CI) <sup>e</sup>	0.76 (0.51-1.13)	1 [Reference]
<b>Diarrhea</b>		
No. of children <sup>a</sup>	1671	1862
No. of visits with diagnosis/total No. of visits	156/11 542	170/12 789
Prevalence, % (95% CI) <sup>d</sup>	1.35 (0.74-1.96)	1.33 (1.03-1.63)
Prevalence ratio (95% CI)	1.02 (0.82-1.26)	1 [Reference]
Adjusted OR (95% CI) <sup>e</sup>	1.07 (0.88-1.28)	1 [Reference]
<b>Respiratory tract infection</b>		
No. of children <sup>a</sup>	1671	1862
No. of visits with diagnosis/total No. of visits	117/11 542	114/12 789
Prevalence, % (95% CI) <sup>d</sup>	1.01 (0.44-1.59)	0.89 (0.37-1.41)
Prevalence ratio (95% CI)	1.14 (0.88-1.47)	1 [Reference]
Adjusted OR (95% CI) <sup>e</sup>	1.21 (0.89-1.63)	1 [Reference]

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

<sup>a</sup>Contributing to the crude analysis.

<sup>b</sup>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.

<sup>c</sup>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, and district.

<sup>d</sup>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.

<sup>e</sup>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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**Financial Disclosures:** None reported.

**Funding/Support:** This study was supported by Médecins Sans Frontières (MSF). Ms Isanaka was supported in part by National Cancer Institute grant R25-CA098566.

**Role of the Sponsor:** MSF reviewed the final study pro-

ocol 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.

**Additional Contributions:** We thank the Ministry of Health of Niger, in particular Amina Yaya, MD (Nutrition Division), and the Regional Public Health Office of Maradi for their support of this project. We thank the field teams of Epicentre and MSF and our dedicated teams of translators, research nurses, and nutrition assistants for their support in gathering data. In particular, we wish to thank the Program Director, Isabelle Defourny, MD (MSF), for her critical and precious insight into the operation of the MSF program in Niger and support of this research and Olivier Cheminat, MSc, Thomas Roederer, MSc, Nael Lapidus, MD, Emmanuelle Robert, MA, and Alexandra Simon, RN (all of Epicentre) for their dedication and work on ensuring the data collection in this study. We also wish to thank Head of Mission Thierry Climat, MA, Medical Coordinator Susan Shepherd, MD, and Field Coordinator Gwenola Seroux, RN, as well as Emmanuel Drouhin, BA (all of MSF), for their help in facilitating this study. André Briend, MD, PhD (World Health Organization), provided important comments on both the protocol and draft of the manuscript. We also sincerely thank Alain Moren, MD, MPH, PhD (Epicentre), Donna Spiegelman, ScD (Harvard School of Public Health), and P. Gregg Grennough, MD, MPH (Harvard Humanitarian Initiative), for their statistical advice and comments. None of these individuals received compensation for this study.

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