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Effectiveness and tolerability of standardized milk based, standardized non-milk based and hospital-based formulations in the management of moderate acute malnutrition in under-five children: A randomized clinical trial

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Abstract*: Introduction*
Moderate acute malnutrition (MAM) is a leading cause of under-five morbidity and mortality globally. Supplementary feeding is a strategy recommended by WHO for managing the condition.
Objective: To evaluate the effectiveness and tolerability of standardized milk-based formulation (SMBF), standardized non-milk based formulation (SNMBF) and hospital-based formulation (HBF) in under-fives with MAM.
Method: This was an open label randomized clinical trial in which eligible children aged 6 – 59 months with MAM were assigned to receive the SMBF, SNMBF or HBF at 50% of their daily caloric requirement with their regular family diet for four months. Their baseline characteristics and anthropometric indices were noted. They were followed up on two weekly basis during which further assessments were performed. The analysis for effectiveness and tolerability of the formulations were based on "per protocol".
Results: A total of 687 children were screened and 188 enrolled. Seventy children received SMBF, 63 received SNMBF while 55 received HBF. There were 54/70 (77.1%), 57/64 (89.1%) and 46/55 (83.6%) evaluable participants in the SMBF, SNMBF and HBF group respectively. Recovery from MAM was 43/54 (79.6%), 40/57 (70.2%) and 32/46 (69.6%) in the SMBF, SNMBF and HBF group respectively. Normal nutritional status was attained by 13 (24.0%), 10 (17.6%) and 5 (10.9%) children in the SMBF, SNMBF and HBF group respectively. Diarrhea and skin rashes were the main features of poor tolerability.
Conclusions: The formulations were effective in managing MAM in childhood but the SMBF was the most effective. Diarrhea and skin rashes were the main features of poor tolerability.

Keyword: nutrition, formulations, follow up, malnutrition, under-fives

Introduction

Moderate acute malnutrition (MAM) is presently a leading cause of childhood morbidity and mortality globally.[1] About 33 million under-fives residing in South Asia, West and Central Africa are moderately malnourished.[2] The condition accounts for about 70.0% of all under-five malnutrition-related deaths globally.[3]

The condition is managed by supplementary feeding using pre-packaged, energy-dense nutritional formulations along with dietary counselling. Ready-to-use supplementary foods (RUSFs) deployed in this condition are known to effective in improving the nutritional status of malnourished children.[4,5] The RUSFs are often supplied on programmatic basis by donor agencies and as such, not readily available in settings where childhood malnutrition is endemic.[6]The non-availability of

these formulations in regions where childhood malnutrition is endemic constitutes a major barrier to the achievement of 40% reduction of childhood stunting and the reduction of childhood wasting to less than 5% as contained in the WHO global nutrition targets of 2025.[7] In settings where childhood malnutrition is prevalent and RUSFs are not readily available, WHO recommends the use of nutrient dense formulations prepared from locally available food stuffs as well as the evaluation of the effectiveness of the formulations.[8] Though improvement in nutritional status has been observed among under-fives with MAM following the use of formulations prepared from locally available food stuffs, there is paucity of empirical data on their effectiveness.[8,9] The management of MAM in childhood is still evolving and there is presently no global consensus on the most appropriate dietary formulation for treating under-fives with the condition.[10]It is therefore necessary to evaluate the effectiveness of locally available nutritional formulations with the potential for managing MAM in a given setting.

The standardized milk-based formulation (SMBF), the standardized non-milk based formulation (SNMBF) and the hospital-based formulation (HBF) are examples of nutritional formulations in the country with potentials for managing MAM in childhood. The SMBF and SNMBF are commercially prepared while the HBF is prepared by the hospital dieticians. The formulations all have maize as the main source of carbohydrate while protein is mainly from milk for the SMBF, soyabeans for the SNMBF and a combination of milk and soybeans in the HBF. Data on the effectiveness and tolerability of these formulations are needed for evidence-based decision in the management of under-fives with MAM in the country.

Objective

To compare the effectiveness and tolerability of SMBF, SNMBF and HBF in the management of children aged 6 – 59 months with MAM.

Outcome measures

Primary: improvement from moderate to mild malnutrition/normal nutritional status (weight-for-height Z-score of +1 to -2 SD) and non-recovery/deterioration to severe acute malnutrition (weight-for-height Z-score between –2 and –3 SD/Z score <-3 SD).
Secondary: tolerability (occurrence of gastrointestinal and extra-intestinal adverse events).

Subjects and methods

Trial design and study area

This was an open label randomized clinical trial conducted from May 2016 – April 2017 in Uruan, Ibiono Ibom and Uyo Local Government Areas (LGAs) of Akwa Ibom State, Nigeria. The LGAs were selected based on the prevalence of MAM in the areas using the 2015 Akwa Ibom State child health survey. The inhabitants are predominantly farmers, fishermen, traders and civil servants. Ibibio and Annang are the languages commonly spoken in the study areas.

Study settings

The study settings were Primary Health Centre (PHC) Adadiah (Uruan LGA), PHC Okopedi use (Ibiono Ibom LGA) and PHC MbakEtoi (Uyo LGA). Each of which was headed by a matron.

Sample size calculation

This was calculated based on non-inferiority of the SMBF/SNMBF compared to the HBF. Using 80% certainty that the lower limit of a 95% two-sided confidence interval will be above the non-inferiority limit of -0.3 assuming a standard deviation of 0.55 units. The minimum sample size obtained was 48 children per group.[11] To make for 10% attrition, the minimum sample size was increased to 53 children per study arm.

Study population

Children aged 6 to 59 months with MAM residing in the selected LGAs. The case definition of MAM was based on weight-for-height/length Z-score between <-2 and -3 SD or mid upper arm circumference (MUAC) of 11.5 cm to 12.5 cm in the absence of oedema.

Eligibility criteria

Children aged 6 – 59 months that met the case definition of MAM were included following parental consent. Those with chronic illnesses (cardiac disease, renal disease, tuberculosis, liver disease or HIV/AIDS), feeding difficulties (gastroesophageal reflux diseases or cleft palate), neurologic disease (cerebral palsy) and diarrheal illnesses were excluded.

Randomization

Balloting technique was used to randomize the participants to the different interventions based on the study sites. The randomization process was implemented by non-members of the research team. Participants enrolled in PHC Adadiah received the SMBF; those enrolled in PHC Okopedi Use received the SNMBF while those enrolled in PHC MbakEtoi received the HBF.

Participant assessment

The basic demographic and clinical information of the children were obtained from their caregivers using a

structured questionnaire. A general physical examination and systemic examination were done. Their anthropometry (weight, MUAC and length/height) was measured using standard techniques.[12]

Investigational products

The investigational products were; the SMBF, SNMBF and HBF.

1) The SMBF was a pre-packaged formulation produced by a reputable food company. The formulation consisted of carbohydrates (mainly maize), proteins (mainly dairy milk), fats, minerals and vitamins. It contained 205 kcal/50g in a 50g sachet.
2) The SNMBF was also produced by a reputable food company. It consisted of carbohydrates (maize), proteins (soya bean), fats, minerals and vitamins. It was contained in 400g tins which had 199 kcal/50g.
3) The HBF was formulated by the hospital dietician. It consisted of carbohydrates (mainly from maize), proteins (soybean and diary milk), fats, vitamin B complex, vitamin C and iron. It was a loose formulation that had 215 kcal/50g. The composition of the formulations is presented in Appendix 1. They were stored at optimal temperature and humidity. The batch number, manufactory and expiry dates of the standardized formulations were verified before being used.

Dietary counselling and food demonstration exercise

The caregivers were counselled on exclusive breast feeding for six months and continuation of breast feeding up to two years age. They were also counselled complementary food preparation using locally available food stuffs, appropriate feeding practice and hand hygiene. Food demonstration exercises using the investigational products with hands-on sessions for the caregivers were conducted.

Administration of investigational products

Each child received an amount of formulation equivalent to 50% of his/her daily caloric requirement based on the intervention arm of his/her assignment along with the regular family diet. Children aged 6-24 months received 100 kcal/kg/day of the formulation assigned to them while those aged 25 – 59 months received 90 kcal/kg/day. The formulations were supplied every two weeks to the caregivers at the health facilities for four months. Those 6-23 months were fed thrice daily with the formulations in addition to breast feeding while those 24-59 months were fed twice daily. The caregivers were instructed not to share the formulations with other members of the household. They were requested to present empty sachets of the formulations which were used as proxies for monitoring adherence to dietary regimen during their biweekly facility visit. They were instructed to note/record unusual gastrointestinal events like vomiting, diarrhea (the passage of ≥ 3 loose stools in 24 hours), abdominal discomfort, constipation, and regurgitation as well as extra-intestinal events during the study period.

Follow-up of participants

The participants were followed up on two weekly basis for four months during which clinical assessment, anthropometric measurement, food demonstration exercise with hands-on sessions were performed. The feeding practices of the caregivers and adverse events of the formulations were noted. Children that developed mild illnesses were treated appropriately by the research team in the community while those with severe illnesses were treated in the UUTH after obtaining the caregiver's consent.

Ethics

Approval for the conduct of the study was obtained from the Health Research Ethics Committee of UUTH and the community chiefs. Parental consent was obtained in writing before inclusion of any eligible child into the study. The trial was registered with the Pan African Clinical Trial Registry with a trial registration number of PACTR201704002119141.

Statistics

Data was analyzed using Stata. Weight-for-height z-score was determined based on the National Center for Disease Statistics, 2000 growth curves. The characteristics of the children were described using frequency and percentage for categorical variables and means with standard deviation for continuous variables. Categorical variables were compared using Pearson's chi-square test (c^2) while the means of continuous variables were compared using ANOVA. The effectiveness and tolerability of the formulations were determined based on 'per-protocol' analysis. Sub-group analysis based on age group was also performed. Statistical tests were deemed significant if p-value was < 0.05.

Results

A total of 687 children were screened and 189 enrolled. Seventy children were assigned to the SMBF but 54/70 (77.1%) completed the study, 64 were assigned to the SNMBF but 57/64 (89.1%) completed the study while 55 were assigned to the HBF but 46/55 (83.6%) completed the study. Fifteen children were withdrawn due to protocol violation while 17 were lost to follow up (Figure 1).

1. Baseline characteristics of study participants

The demographic and anthropometric parameters of the

Table 1: Baseline clinical characteristics of study participants

Characteristics of participants	Interventions arms			
	Milk based formulation N = 70	Non-milk based formulation N = 64	Hospital-based formulation N = 55	P value
Gender				
Male	38	22	25	
Female	32	42	30	
Mean age (months)	17.1 ±10.86	22.6±14.56	19.09± 11.60	0.1616
Mean weight (Kg)	7.80±2.01	8.14±2.10	8.12 ± 1.96	0.6723
Mean height/length (cm)	76.15 ± 9.88	77.3 ± 9.99	76.88±10.07	0.8442
MUAC (cm)	12.29±1.09	12.27±0.78	12.45 ± 0.90	0.306

MUAC = Mid Upper Arm Circumference

2. *Effect of standardized milk-based compared to hospital-based formulation on MAM*

The recovery from moderate acute malnutrition (MAM) for all age categories was 79.6% (43/54) in the children treated with the SMBF as against 69.6% (32/46) in those treated with the HBF as seen in Table 2. There was a higher recovery with the SMBF compared to the HBF in the age categories of 6 – 23 months and 24 – 59 months as displayed in Table 2.

3. *Effect of standardized non milk based compared to hospital-based formulation on MAM*

The recovery from MAM for all age categories treated with the SNMBF was 70.2% (40/57) as against 69.6% (32/46) in the HBF group. In infants and young children, the recovery from MAM was higher with the HBF than SNMBF while the converse was the case in those 24 – 59 months as shown in Table 3.

Table 2: Effect of Milk based formulation compared to Hospital-based formulation on MAM

Outcome	Milk based formulation	Hospital-based formulation	Test for significance
All Under-fives (6-59 months)	N=54	N=46	
Recovery from MAM	43 (79.6%)	32 (69.6%)	$\chi 2 = 1.3419$
No improvement or worse	11 (20.1%)	14 (30.4%)	p = 0.2466 RR=1.14(0.91-1.45)
Infants and young children (6 - 23 months)	N=42	N=33	
Recovery from MAM	34 (80.9%)	25 (75.7%)	$\chi 2 = 0.2972$
No improvement or worse	8 (19.1%)	8 (24.3%)	p = 0.5881 RR=1.07(0.84-1.36)
Children aged 24 -59 months	N = 12	N = 13	
Recovery from MAM	9 (75.0%)	7 (53.8%)	*F= 0.411
No improvement or worse	3 (25.0%)	6 (46.2%)	RR = 1.39 (0.76-2.54)

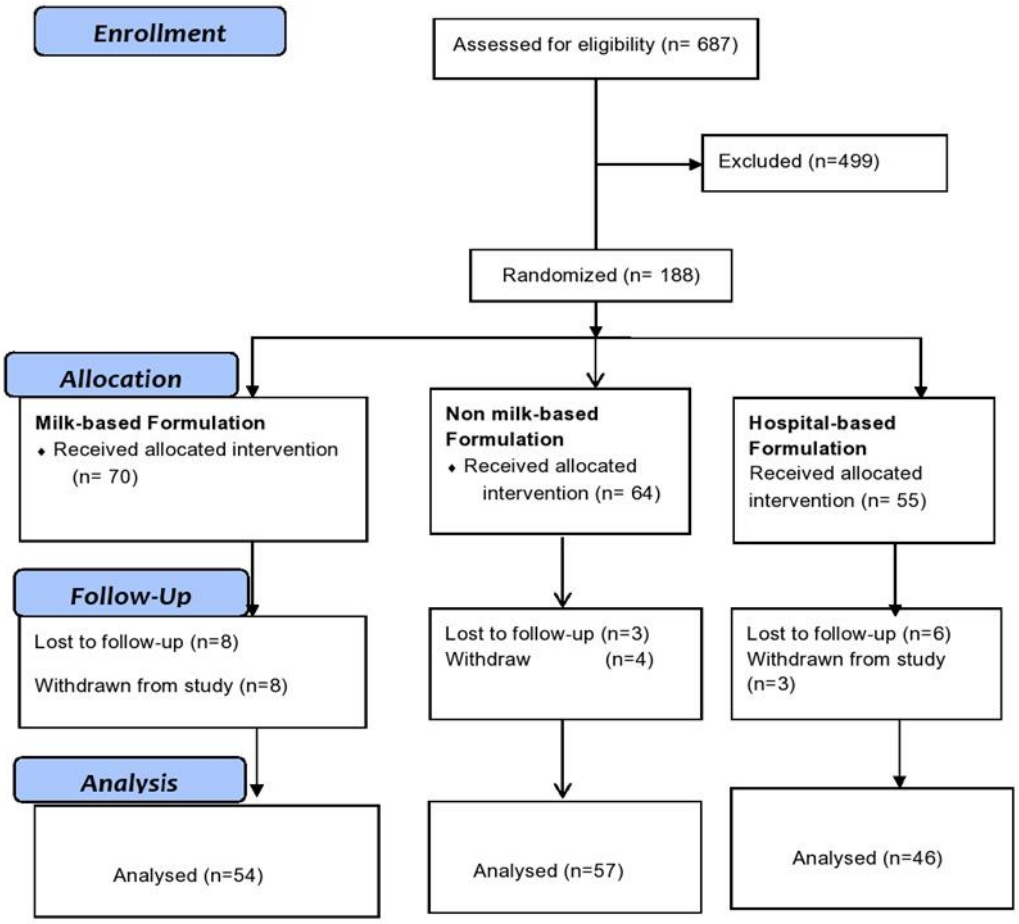
MAM = Moderate acute malnutrition *Fisher's exact test

Table 3: Effect of standardized non-milk based formulation compared to hospital-based formulation on MAM

Outcome	Standardized Non-Milk based formulation	Hospital-based formulation	Test for significance
All Under-fives (6-59 months)	N=57	N=46	
Recovery from MAM	40 (70.2%)	32 (69.6%)	$\chi^2 = 0.0045$
No improvement or worse	17 (29.8%)	14 (30.4%)	p = 0.9464 RR=1.52(0.97-2.38)
Infants and young children (6 -23 months)	N=37	N=33	
Recovery from MAM	25 (67.6%)	25 (75.7%)	$\chi^2 = 0.5733$
No improvement or worse	12 (32.4%)	8 (24.3%)	p = 0.4489 RR=0.89 (0.66-1.20)
Children aged 24 – 59 months	N = 20	N = 13	
Recovery from MAM	15 (75.0%)	7(53.8%)	F = 0.269
No improvement or worse	5 (25.0%)	6 (56.2%)	RR=1.39 (0.79-2.45)

MAM = Moderate acute malnutrition

Fig 1: Flow diagram of study profile



4. Effect of nutritional formulations on full catch-up growth of study participants

The overall recovery from MAM was 73.2% (115/157). Full catch-up growth was observed in 17.8% (28/157) of the participants. Recovery from MAM with catch-up growth was highest among those that received the SMBF, 24.0% (13/54) and least 10.9% (5/54) in those that received the HBF. The difference in proportion of full catch-up growth in the various groups was not statistically significant ($\chi^2 = 2.961$; $p = 0.228$)as shown in Table 4.

Table 4: Attainment of full catch-up growth based on nutritional formulation

Nutritional intervention group	Attainment of full catch up growth
Standardized milk-based formulation (N = 54)	13 (24.0%)
Standardized non milk-based formulation (N = 57)	10 (17.6%)
Hospital-based formulation (N = 46)	5 (10.9%)

Full catch-up growth: weight-for-height Z-score of +1 to -1 SD

The main features of poor tolerability were diarrhea and report of skin reaction. The occurrence of diarrhea was comparable in the different groups ($\chi^2 = 0.169$; $p = 0.918$). The report of skin reaction was highest (16.7%) in the SMBF group and lowest (2.2%) in in the HBF group.

Table 5: Tolerability of formulations among study participants

Features of tolerability	Milk based formulation 54	Non-milk based formulation 57	Hospital-based formulation 46
Diarrhoea	6 (11.1%)	6 (10.5%)	4 (8.7%)
Regurgitation	0 (0%)	4 (7.0%)	0 (0%)
Vomiting	1 (1.9%)	1 (1.8%)	1 (2.2%)
Abdominal colic	2 (3.7%)	0 (0.0)	0 (0%)
Skin rash	9 (16.7%)	3 (5.3%)	1 (2.2%)

Discussion

The effectiveness of standardized milk-based formulation (SMBF), standardized non-milk based formulation (SNMBF) and hospital-based formulation (HBF) at 50%

of the daily caloric requirement of under-five children with moderate acute malnutrition (MAM) while on their regular family diet for four months was 79.6%, 70.2% and 69.6% respectively. The effectiveness of the SMBF on MAM in this study is similar to the 80.0% and 79.1% reported by Matilksy et al[13] in Malawi and Nacker et al[14] in Niger but slightly higher than 73.0% reported in Ethiopia by Karakochuk et al[15]among a similar category of children treated with a Lipid Nutrient Supplement (LNS).

The effectiveness of the different nutritional formulations in this study is lower than the 85% reported by Medoua et al[16]in Cameroun among children aged 25 – 59 months that were treated for two months with a LNS but comparable to 73.0% recovery reported in those treated with a Corn Soy Blend. The difference in recovery from MAM between participants in this study and that of Medoua et al[16]could be attributed to the difference in the type of formulations used for feeding the children. Lipid-containing formulations are likely to provide more energy that would positively impact on growth and recovery from malnutrition when compared to formulations without lipids.

The variation in the protein source and micronutrient content of the formulations might also have influenced the outcome of this study. The SMBF contained milk (animal protein) which is usually of high biological value, the SNMBF contained soybeans (plant protein) which is usually deficient in one or more of the indispensable amino acids while the HBF contained milk and soybeans (combination of animal and plant protein). Adequate intake of protein of high biological value (animal protein) is recommended for actively growing children.[17]Thus, the highest recovery from MAM was expected in children treated with the SMBF and the least in those treated with SNMBF. As expected, those treated with the SMBF had the highest recovery but contrary to our expectation, there was no difference in recovery between the HBF and SNMBF groups. The relatively high concentration of micronutrients (calcium, vitamin D and zinc) in the standardized formulation (SMBF/ SNMBF) compared to the HBF might have contributed to this finding. Calcium and vitamin D are important for skeletal growth while zinc is known to improve growth and immunologic function.[18] Hence, children that received the SMBF or SNMBF were more likely to improve in linear growth than those that received the HBF.[18] The positive impact of protein source on recovery in the HBF group versus the SNMBF group might have been equilibrated by the relatively high micronutrient composition of the SNMBF when compared to the HBF resulting in no detectable difference in effectiveness between both formulations.

Another possible reason for the lack of detectable difference in effectiveness between the HBF and SNMBF is the duration of the study. An appreciable change in the axial growth but not linear growth could be observed within a period of four months in clinical trials evaluating nutritional formulations for malnourished children.[19] However, to appreciate the effect of nutritional formulations on linear growth, an intervention period much longer than four months is required. Some studies that detected significant difference in effect of formulations on linear growth were conducted for six months and beyond.[10]

Besides, the appreciable overall recovery from MAM in the different groups; a small proportion of children in each group achieved full catch-up growth with the SMBF group having the highest (24.0%). Intervention in childhood nutrition within the first 1000 days is known to be quite critical to the attainment of the full catch-up growth and development potential of children. This period is recognized as a window of opportunity for instituting targeted interventions aimed at preventing or reversing nutritional deficiencies and functional impairments in young children.[20] The attainment of full catch-up growth in children with MAM reduces the risk of relapse to MAM in settings of persistent household food insecurity when compared to those that attain a modest recovery from MAM without achieving full catch-up growth within the intervention period.[21] Full catch-up growth does not only impact on the physical growth parameters and nutritional status of children but also impacts positively on their immunologic, metabolic and cognitive functions.[1]

The main features of poor tolerability of the formulations were diarrhea which occurred in a similar frequency across the three intervention arms and skin rash which was reported mainly in the SMBF group. The incidence of vomiting was also similar in the different groups. Cochrane systematic reviews that evaluated the effect of LNS and CSB in the management of under-fives with MAM reported similar occurrence of diarrhea in both groups with the use of LNS and CSB but a higher frequency of vomiting among those managed with LNS than those managed with CSB.[5,22]

In view of the nutritional crisis of children residing in low-/middle income countries, the increasing burden of MAM and the several life-threatening complications associated with the condition, large-scale community-based supplementary feeding of under-five children with MAM using any of the evaluated formulations in this study will go a long way to enhance their recovery thereby reducing childhood mortality in the region. Further research at bridging the existing micronutrient gap regarding linear growth in the HBF is needed to optimize its effect.

This study provides evidence on the effectiveness and tolerability of some of the locally available nutritional formulations for managing MAM in under-fives in the country. Large scale studies are needed not only to confirm this but to also to thoroughly investigate the observed adverse events of the formulations.

Conclusions

The use of SMBF, SNMBF or HBF at 50% of the daily caloric requirements of children aged 6 – 59 months with MAM was quite effective in managing the condition. The highest recovery from MAM and attainment of full catch-up growth was observed in those treated with the SMBF, while the SNMBF and HBF were of comparable effectiveness. The main features of poor tolerability were diarrhea and skin rashes. Any of these formulations could be deployed for large scale use in regions where MAM in childhood is endemic.

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Authors Contributions
The study was conceived by Ekong Udoh and supervised by Martin Meremikwu. Ekong Udoh, Blessing Nwazuluoke, Victor Bassey, Regina Ejemot-Nwadiaro and Martin Meremikwu prepared the protocol, study design and data collection tools. Blessing Nwazuluoke, Victor Bassey, OlugbemiMotilewa and Ekong Udoh collected the data which was analyzed by OlugbemiMotilewa, Regina Ejemot-Nwadiaro, Ekong Udoh and Martin Meremikwu. Data interpretation was done by Martin Meremikwu, Blessing Nwazuluoke, Victor Bassey, OlugbemiMotilewa and Ekong Udoh. All the authors contributed to the write up of manuscript and approved the final version.
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Appendix 1: Comparison of nutrient composition of the different formulations

	Cereal-based formulation (Standardized milk-based formulation)		Soya-Cereal based formulation (Standardized non-milk based formulation)		Hospital-based formulation	
Average Nutrient Composition (unit)	Per meal (50g=200ml)	% RDA	Per meal (50g=200ml)	% RDA	Per meal 200ml	RDA %
Energy (Kcal)	205	29	199	29	214.7	31.3
Fat (gm)	5	17	4.5	15	10.7	35.7
Linoleic acid (gm)	0.75	16	1.7	37	1.89	41.14
Protein (gm)	7.5	68	7.5	68	7.2	65.28
Carbohydrate (gm)	32.5	34	32.1	34	22.08	23.39
Dietary fibre (mg)	2.15	43	3.5	70	0.15	3.0
Vit. A (IU)	650	130	750	150	555	111
Vit. D (IU)	100	50	100	50	40	20
Vit. E (IU)	3.4	68	3.4	68	1.97	39.4
Vit. C (mg)	25	50	25	50	43.6	87.2
Vit. B1 (mg)	0.3	100	0.4	133	0.421	140
Vit. B2 (mg)	0.37	94			0.602	152.9
Niacin (mg)	1.5	38	2.0	50	4.78	123.37
Vit. B6 (mg)	0.5	50	0.15	50	0.031	3.1
Folic Acid (µg)	20	25	40.0	50	41.0	51.3
Vit. B12 (µg)	0.55	110	0.4	80	0.32	64
Calcium (mg)	300	111	195	72	128.79	47.65
Sodium (mg)	72.5	36	105	53	48.7	24.58
Iron (mg)	3.8	35	5.0	45	3.23	29.58
Zinc (mg)	3.0	100	3.0	100	0.384	12.8