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Effectiveness of a nonweight-based daily dosage of ready-to-use therapeutic food in children suffering from uncomplicated severe acute malnutrition: A nonrandomized, noninferiority analysis of programme data in Afghanistan

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Abstract

Severe acute malnutrition (SAM) remains a major global public health problem. SAM cases are treated using ready-to-use therapeutic food (RUTF) at a dosage of ~200 kcal/kg/day per the standard treatment protocol (STD). Emerging evidence on simplifications to the standard protocol, which among other adaptations, includes reducing the daily RUTF dosage, indicates that it is effective and safe for treating children with SAM. In response to a foreseen stock shortage of RUTF, the government of Afghanistan endorsed the temporary use of a modified treatment protocol in which the daily RUTF dosage was prescribed at 1000 kcal/day (irrespective of body weight) until the child achieved moderate acute malnutrition status (weight-for-height *z*-score ≥ −3 or mid-upper arm circumference [MUAC] ≥ 115 mm), at which point 500 kcal/day was prescribed until cured (modified treatment protocol [MTP]). In this paper, we report the results of this nonweight-based daily RUTF dosage experience. Data of 2042 children with SAM, treated using either the STD protocol ($n = 269$) or the MTP protocol ($n = 1773$) from August 2019 to March 2021 in five provinces, were analyzed. The per-protocol analyses confirmed noninferiority of MTP protocol when compared to STD protocol for recovery rate [93.3% vs. 90.2%; Δ (95% confidence interval, CI) = 3.1 (−0.9; 7.2) %] and length-of-stay [82.6 vs. 75.6 days; Δ (95% CI) = 6.9 (3.3; 10.5) days], considering the margin of noninferiority of −10% and +14 days, respectively. Weight gain velocity was smaller in the MTP protocol group than in the STD protocol group [3.7 (1.7) vs. 5.2 (2.9) g/kg/day; Δ (95% CI) = −1.5 (−1.8, −1.2); $p < 0.001$]. The STD group had a significantly higher mean than the MTP group for absolute MUAC gain [Δ (95% CI) = 1.7 (1.0; 2.3) mm; $p < 0.001$] and the MUAC velocity [Δ (95% CI) = 0.29 (0.20; 0.37) mm/week; $p < 0.001$]. Our results confirm the noninferiority of a

nonweight-based daily dosage and support the endorsement of this modification as an alternative to the standard protocol in resource-constrained contexts.

KEYWORDS

Afghanistan, community-based, effectiveness, management of acute malnutrition, noninferiority, ready-to-use therapeutic food, reduced dosage, severe acute malnutrition, simplified protocol, single dosage, wasting

1 | INTRODUCTION

Undernutrition, including wasting and nutritional oedema, remains a major global public health concern with low- and middle-income countries from Africa and Asia being the most affected (Black et al., 2013; Khalid et al., 2019; Micha et al., 2020; Mutunga et al., 2020; Neufeld et al., 2020). Globally, wasting, a form of acute malnutrition, affected around 45 million children below 5 years of age in 2022 (United Nations Children's Fund (UNICEF); World Health Organization [WHO]; International Bank for Reconstruction and Development/The World Bank, 2023). This figure does not include children who suffered from nutritional oedema, hence underestimates the actual global burden of undernutrition as this form of severe undernutrition is usually omitted in national and global statistics while still prevalent in several countries (Alvarez et al., 2016). In all affected countries, undernutrition leads to serious public health risks and developmental and economic loss (Bagriansky et al., 2014; Black et al., 2013; Grey et al., 2021; Kirolos et al., 2022). Wasting contributes to over one million deaths of children of that age group worldwide (Headey et al., 2020; Osendarp et al., 2021). Indeed, its severe form is associated with an increased near-term mortality risk (McDonald et al., 2013; Olofin et al., 2013). A child with severe acute malnutrition (SAM) is up to 12 times more likely to die than a well-nourished child (McDonald et al., 2013; Olofin et al., 2013). A significant proportion of survivors sustain many sequelae affecting their development, long-term health conditions and economic production capacity (Kirolos et al., 2022). Thus, prevention, early diagnosis and treatment of wasting must be prioritized (WHO, FAO, UNHCR, UNICEF, & WFP, 2020).

As per the most recent national prevalence estimate from 2013, 9.5% of children under 5 years of age suffer from wasting in Afghanistan (National Nutrition Survey Afghanistan Report, 2013). In 2019, it was estimated that two million children under 5 years of age suffered from wasting at any point of time, of whom six hundred thousand were severely wasted, therefore requiring treatment with ready-to-use therapeutic food (RUTF) using the Integrated Management of Acute Malnutrition (IMAM) protocol. The IMAM programme was specifically designed to improve child mortality risk, improve nutrition outcomes and increase coverage of treatment for children with wasting (Collins, 2007; WHO, WFP, UNICEF, & UNSCN, 2007). The coverage of IMAM services has been steadily increasing in Afghanistan. A total of 62,000 children were treated nationwide in 2012 and over 275,000 children were treated in 2018, corresponding to a rise from 19% to 50% coverage rate of children suffering from severe wasting treatment (Qarizada et al., 2018). Despite this progress, the country has not yet reached the global target in terms of treatment coverage due to several challenges, including financial resources constraints (Qarizada et al., 2018). In 2019, this financial constraint translated into a shortage of RUTF in comparison to the anticipated caseload. In response to this constraint, the Ministry of Public Health (MoPH), in consultation with partners, authorized the use of a modified treatment protocol, which piloted a nonweight-based daily dosage of RUTF, to ensure an increase in coverage, thereby allowing more children to be treated.

Key messages

- More evidence supporting the use of the nonweight-based daily ready-to-use therapeutic food (RUTF) dosage for treating uncomplicated severe acute malnutrition (SAM), in specific contexts, is needed.
- Our real-world prospective nonrandomized study showed that the fixed nonweight-based daily RUTF dosage protocol is as effective as the standard weight-based protocol for treating uncomplicated SAM in children <5 in the Afghanistan context.
- Our findings support the reflection of a nonweight-based daily RUTF dosage in resource-constrained contexts in national and global policies and guidelines to improve coverage of all children in need of treatment.

The simplified approaches (referred to as simplified protocols in some contexts) refer to a number of different adaptations to existing national and global protocols for the management of acute malnutrition, which have been designed to address context-specific barriers to treatment coverage and improve the efficiency of acute malnutrition treatment services (Buttarelli et al., 2021; Sophie Woodhead & Zagre, 2019a). Reduction of the daily dose of RUTF, which is nonweight-based and varies according to the child's weight on admission, is among the promising modifications being tested, and has already been successfully applied in research and operational contexts with encouraging results (UNICEF, 2021). One of the aims of this modified RUTF daily dosage is to improve the efficiency of wasting treatment programmes without compromising on its effectiveness

(Action Against Hunger USA, 2021; UNICEF, 2021). While in some contexts this modification is implemented in combination with other simplifications to treatment protocols (e.g., use of a single product to treat both SAM and moderate acute malnutrition (MAM), reduced follow-up visits, expanded admission criteria), it is this adaptation that the Afghan MOPH decided to pilot during the 2019 RUTF stock crisis under a revised protocol. It is important to note the reduced visits modification was also introduced into both treatment protocols in 2020 during the COVID-19 pandemic.

This paper describes findings from this particular modified dosage experience, with the objective to confirm noninferiority in terms of nutrition outcomes, specifically recovery rate, and length of stay (LOS). Secondary outcomes of interest included weight and MUAC growth in terms of absolute gain and velocity. By reporting our findings, we are hoping to contribute to the evidence for this adaptation to global protocols for child wasting. This is of particular relevance given the low certainty evidence used for the formulation of the new recommendation on daily RUTF dose for treating children with severe wasting or nutritional oedematous malnutrition included in the newly released 'WHO guideline on the prevention and management of wasting and nutritional oedema (acute malnutrition)' (World Health Organization, 2023).

2 | METHODS

2.1 | Study design

The study is a real-world prospective nonrandomized study assessing the noninferiority of a modified RUTF daily dosage when compared to the standard weight-based daily dosage of RUTF. The prescribed daily dosage, under the modified treatment protocol (MTP), was 1000 kcal per day of RUTF to all children, irrespective of body weight, during the SAM phase of the disease (MUAC < 115 mm or weight-for-height *z*-score [WHZ] < −3) and a shift to 500 kcal per day, irrespective of body weight, when the child reached the MAM case-definition (MUAC ≥ 115 mm or WHZ ≥ −3). Children under this treatment protocol are referred to as the MTP Group. The standard treatment protocol (STD) group included children prescribed a body weight-based daily dosage of RUTF, as per the national IMAM guidelines, and a group of children prescribed 1000 kcal per day irrespective of body weight throughout the entire treatment period, for whom this dosage provided ≥150 kcal/kg/day. Children of the STD group who were prescribed the body-weight-based daily dosage came from one province only (Nangarha), while children receiving the ≥150 kcal/kg/day dosage came from all the provinces surveyed. Children enroled were followed-up weekly before the onset of the COVID-19 pandemic and fortnightly during the pandemic period. Both study groups included children followed-up weekly and children followed-up fortnightly.

These data were prospectively collected during the pilot phase of the experimentation of the MTP protocol using specially designed data collection tools under the supervision of specially employed pilot programme supervisors. The main role of the supervisors was to strengthen the quality of data including accuracy of information and measurements, completeness of data collected and accuracy and completeness of data recording and storing.

2.2 | Acquisition and source of data

The original dissemination plan did not include the publication of findings in a peer-reviewed journal. Special authorization had to be requested. UNICEF obtained the authorization to use the data and publish the findings from the relevant national authorities before sharing the data. An anonymized individualized data set was used for this analysis, provided in Excel format from the UNICEF Afghanistan Country team. Analysis was conducted after a thorough data control and a series of quality checks including assessment of biological plausibility of age, weight, length/height and nutritional indices and adherence to the allocated study treatment protocol, performed by the UNICEF nutrition country team and the data analyst. The biological plausibility of the nutritional indices was checked using the WHO flags criteria (de Onis et al., 2006).

2.3 | Setting and study population

Data were collected in the Daikundi, Kapisa, Kunar, Nangarhar and Parwan provinces of Afghanistan. The study population included all children 6–59 months enroled in an IMAM programme in these provinces, from August 2019 to March 2021. The data were collected from health facilities that were supposed to use both MUAC and WHZ as independent indicators for admitting children in IMAM programme, as recommended by the national guidelines. However, the analysis of the nutrition parameters of admission suggests that these health facilities were predominantly operating as a MUAC-only (and oedema) programme. This deduction is based on the low proportion of children admitted with WHZ < −3 given the known epidemiologic profile of children under 5 with acute malnutrition in Afghanistan (Humphreys et al., 2019).

2.4 | Principal outcomes

The study's principal outcomes for which noninferiority was assessed included the recovery rate and LOS. Secondary outcomes of interest included absolute weight gain and weight gain velocity, absolute MUAC gain and MUAC velocity, and weight and MUAC longitudinal trajectories.

2.5 | Sample size

The sample size was not predetermined. It was decided to use the data of all children enroled during the predetermined period of data collection from August 2019 and March 2021.

2.6 | Data management

Data management at the time of starting data analysis involved the conversion of the data set from Excel format to STATA format. The STATA file was used for data re-cleaning to verify accuracy of conversion, variables transformation and creation of new variables. The final step of the management of the data was the creation of two clean datasets, one in wide format and the second in long format. The long format allowed for the organization of time in the programme in weeks since admission (variable visits converted in weeks elapsed since admission).

2.7 | Statistical analyses

Statistical analyses were performed with STATA (ver. 14.0; StataCorp.). Standard quantitative statistics were used for describing the variables and making the basic comparison between the STD and the MTP groups. Noninferiority was assessed using the approach based on the confidence interval of the difference between the experimental and the control arms as proposed in the literature (Kaul & Diamond, 2006; Pigeot et al., 2003). For recovery rate, the noninferiority was assessed using both the intention-to-treat (ITT) and per-protocol (PP) analyses and results presented. Weight gain velocity and LOS were calculated using only data from children who recovered, the unadjusted and adjusted linear regression mixed effects modelling analyses estimates were used for assessing noninferiority (Mascha & Sessler, 2011). Multilevel linear regression mixed effects modelling was used to estimate the longitudinal response to treatment with the STATA commends margins and margins plot used to depict the trends in predicted values of the anthropometric parameters of interest (weight or MUAC). The adjustment variables included in the model included sex, age and anthropometry at admission (weight, MUAC and HAZ).

2.8 | Definitions

The final treatment outcomes were defined as recommended by the national IMAM guidelines and included the categories of recovery, default, nonrecovery, transfer-out to an inpatient facility, transfer-out to another outpatient facility and death. The definition of recovery varied according to the admission indicators. For children admitted by the MUAC case definition of SAM only, the anthropometric criterion of recovery was reaching MUAC ≥ 125 mm. For children admitted by the WHZ SAM case definition, the recovery criterion was reaching WHZ ≥ −2. For children who met both MUAC and WHZ SAM case definitions at admission, the recovery criteria was reaching MUAC ≥ 125 mm and WHZ ≥ −2. Children who recovered were discharged if the recovery criterion was met for two consecutive follow-up visits regardless of the follow-up visit frequency being used (weekly or fortnightly). The absolute weight gain was defined as the total weight increment in kilogram (kg) from admission to exit. Overall weight gain velocity (from admission to exit) was calculated by dividing the absolute weight gain expressed in grams by the weight at admission kg and the LOS in days. The LOS was calculated as the number of days elapsed from admission to exit, irrespective of having or not missing follow-up visits in between and regardless of the type of final outcome. A child was considered as a defaulter if they missed three consecutive follow-up visits (as per the site visit frequency). A child was considered as nonrecovered if they remained in treatment for 4 months without reaching the recovery criteria.

2.9 | Ethical considerations

This paper is based on data collected as part of IMAM monitoring and evaluation activities for which prior ethical approval and protocol registration are not mandatory. However, authorization to analyze the data and publish findings was sought and obtained from Afghanistan's MoPH, Public Nutrition Directorate at the time of manuscript development. Given the situation in Afghanistan, there was no functional national ethical committee in place to provide formal ethical clearance.

3 | RESULTS

3.1 | General characteristics of participants

Data of 2391 children enroled in IMAM programme in Daikundi, Kapisa, Kunar, Nangarhar and Parwan provinces, from August 2019 to March 2021, were available of whom 349 were excluded for having nutritional oedema (very small number) or because of a different daily RUTF dosage than the one being tested (Figure 1). The final sample for analyses was 2042 severely wasted children treated either using the standard treatment protocol ($n = 269$) or the modified treatment protocol ($n = 1773$). The sample included more girls (1276/2042 = 62.5%) than boys (766/2042 = 37.5%), but there was no difference in sex distribution between the two groups [% of girls was 63.9% in the STD group vs. 62.3% in the MTP group; $p = 0.597$]. Over 90% of children in the sample were below 24 months of age with the overall and group median being below 12 months (Table 1). This median was significantly lower in the STD group than in the MTP group (Table 1). The overall mean (SD) of admission weight was 6.2 (1.2) kg. Children of the STD group were lighter than those of the MTP group [5.7 (0.8) kg for the STD group vs. 6.3 (1.2) kg for the MTP group; $p < 0.001$]. For the stature, the overall mean of admission height was 66.4 (6.8) cm with children of the STD group being shorter than those of the MTP group [64.0 (4.3) cm for the STD group vs. 66.8 (7.0) cm for the MTP group; $p < 0.001$]. Additional nutritional characteristics of admission are shown in Table 1 below.

Overall, 76.0% (1551/2042) of children in the analyzed sample met only the MUAC SAM case definition. This percentage was 73.6% (198/269) among children of the STD group and 76.3% (1353/1773) among those of the MTP group ($p = 0.333$). Over 90% and 100% of these children received a reduced daily dosage of RUTF during the SAM phase and MAM phase, respectively (Table 2).

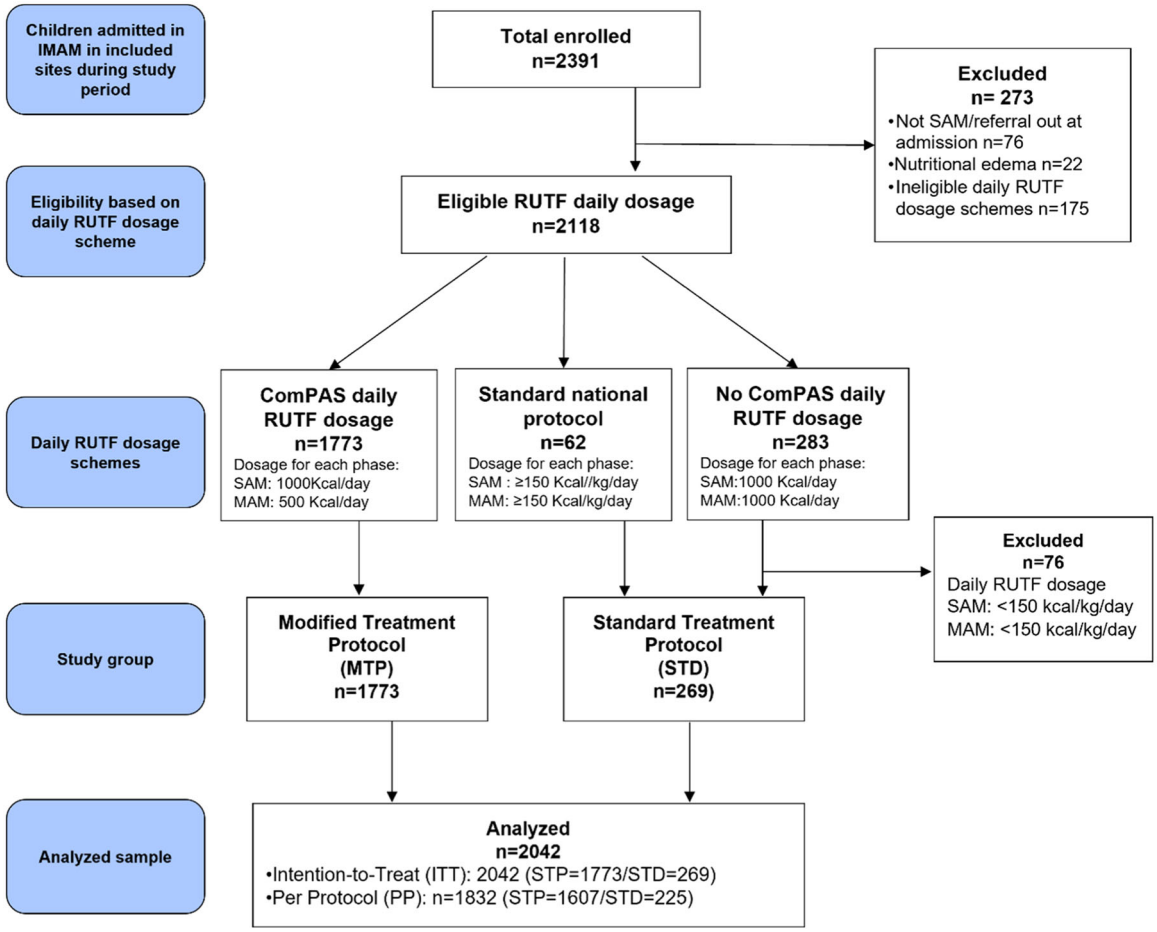

FIGURE 1 Study inclusion flowchart. ComPAS, Combined Protocol for Acute Malnutrition Study; MAM, moderate acute malnutrition; IMAM, Management of Acute Malnutrition; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition.

3.2 | Primary outcomes

3.2.1 | Recovery rate and other nutrition outcomes

Table 3 below presents the principal final treatment outcome. It shows that for both the ITT and PP analyses, the recovery rate met the minimum SPHERE standards (Sphere Association, 2018). Both groups met the minimum SPHERE standards for mortality rate and default rate though had higher nonrecovery rates than the internationally recognized minimum.

As shown in Figure 2, the ITT and PP analyses confirmed the noninferiority of the modified treatment protocol when compared to the standard nutrition protocol for the recovery rate.

3.2.2 | LOS

The mean (SD) LOS for the 1703 children who were discharged as recovered was 81.7 (23.1) days. It was 82.6 (22.8) days for the MTP group and 75.6 (24.8) days for the STD group. The difference confirmed the noninferiority of MTP protocols when compared to STD protocols, both when the conclusion is based on the unadjusted estimate and when the estimate is adjusted for age, sex, MUAC and weight of admission and presence of stunting (Figure 3).

3.3 | Secondary outcomes

3.3.1 | Weight gain

The overall mean (SD) absolute weight gain and weight velocity for all children discharged (n = 2042/2021) were 1.622 (0.842) kg and 3.50 (1.27) g/kg/day, respectively. The figures for the analysis restricted to children who recovered (n = 1703) were 1.837 (0.683) kg and 3.89 (1.97) g/kg/day, respectively. The comparison of the recovered children from the MTP group to those from the STD group yielded a small but significant absolute weight gain difference [mean (SD) = 1.812 (0.641) kg for the MTP group vs. 2.017 (0.921) kg for the STD group, Δ (95% CI) = −0.204 (−0.304, 0.105), p < 0.001]. After adjustment for age, weight and MUAC of admission and sex, the difference became nonsignificant [Δ (95% CI) = −0.057 (−0.311, 0.055) kg; p = 0.317]. Regarding weight growth velocity of the

TABLE 1 Demographic and neutrino characteristics at baseline of children enroled into the study, by study group.

Variable	All children (*n* = 2042) *n* (%)	STD protocol (*n* = 269) *n* (%)	MTP protocol (*n* = 1773) *n* (%)	*p* Value[a]
Age				
Median (IQR), *m*	10 (8–15)	9 (8–12)	10 (8–16)	0.001
<12 months	1177 (57.6)	178 (66.2)	999 (56.3)	
12–23 months	694 (34.0)	78 (29.0)	616 (34.74)	0.004
24 months	171 (8.4)	13 (4.8)	158 (6.0)	
Total	2042 (100.0)	269 (100.0)	1773 (100.0)	
Weight-for-height z-score[b]				
Mean (SD)	−2.04 (1.24)	−2.16 (1.25)	−2.03 (1.24)	0.110
≥−2	987 (48.3)	129 (48.0)	858 (48.4)	
≥−3 and <−2	584 (28.6)	73 (27.1)	511 (28.8)	0.706
<−3	471 (23.1)	67 (24.9)	404 (22.8)	
Total	2042 (100.0)	269 (100.0)	1773 (100.0)	
Mid-upper arm circumference (mm)				
Mean (SD), mm	110.0 (5.60)	108.8 (7.0)	110.4 (5.3)	<0.001
≥125 mm	22 (1.1)	6 (2.3)	16 (0.9)	
115–124 mm	77 (3.8)	14 (5.2)	63 (3.6)	0.055
<115 mm	1941 (95.1)	248 (92.5)	1693 (95.5)	
Total	2040 (100.0)	268 (100.0)	1772 (100.0)	
Height-for-age z-score[b]				
Mean (SD)	−3.16 (1.64)	−3.55 (1.66)	−3.10 (1.63)	<0.001
≥−2	484 (23.7)	45 (16.7)	439 (24.8)	
≥−3 and <−2	511 (25.0)	56 (20.7)	455 (25.7)	<0.001
<−3	1047 (51.3)	168 (62.5)	879 (49.6)	
Total	2042 (100.0)	269 (100.0)	1773 (100.0)	

Abbreviation: IQR, interquartile range.

[a]Student's *t*-test used for the comparison of means, Kruskal–Wallis test used for the comparison of medians, and Pearson's χ^2 test used for the comparison of proportions.

[b]Calculated using the 2006 World Health Organization growth standards.

recovered children, the MTP group had a mean of 3.7 (1.7) g/kg/day and the STD group a mean of 5.2 (2.9) g/kg/day in the unadjusted analysis [Δ (95% CI) = −1.5 (−1.8, −1.2); $p < 0.001$]. The difference remained significant after adjustment for the same variable as above [Δ (95% CI) = −1.0 (−1.4, −0.6); $p < 0.001$].

3.3.2 | MUAC change

The mean (SD) absolute MUAC gain and MUAC velocity for children discharged as recovered for the entire sample (*n* = 1701) were 15.90 (4.76) mm and 1.70 (0.57) mm per week, respectively. The STD group (*n* = 202) had a significantly higher mean than the MTP group (*n* = 1499) for both the absolute MUAC gain [mean (SD) = 17.40 (6.81) vs. 15.70 (4.38) mm; Δ (95% CI) = 1.70 (1.00; 2.40) mm; $p < 0.001$] and the MUAC velocity [mean (SD) = 1.70 (0.66) vs. 1.41 (0.55) mm per week; Δ (95% CI) = 0.29 (0.20; 0.37) mm per week; $p < 0.001$].

3.3.3 | Weight and MUAC trajectories

Figure 4 below presents the longitudinal trajectories of weight (Figure 4a) and MUAC (Figure 4b) during treatment as predicted by a multilevel linear regression mixed effect modelling including sex, age, weight, MUAC and HAZ at admission as adjusting variables. It shows

that for both weight and MUAC velocity did not differ across groups during the first 4 weeks of treatment. Afterwards, the rate of catch-up growth of children of the MTP group became smaller than that of the STD group. The proportion of children receiving the unique dose of RUTF of 500 kcal/day among children of the MTP group reached 48.5% at Week 4 and 77.8% at Week 6.

4 | DISCUSSION

The main objective of our analysis was to confirm the noninferiority of the MTP in terms of recovery rate and LOS. Our results confirm that the MTP model that included a nonweight-based RUTF daily dosage modification and a unique RUTF dosage (1000 Kcal during SAM phase and 500 Kcal/day during MAM phase), resulting in a reduced daily RUTF dosage both during SAM and MAM phases for a substantial proportion of children of this study, was not inferior to STD by the recovery rate and LOS criteria. The results were inconclusive for the secondary outcome of weight growth in terms of absolute weight gain and weight gain velocity. Although the STD group had higher values, the observed differences were not clinically relevant and therefore could not be the basis for conclusions regarding negative effect on weight growth. Our results also showed that the weight and MUAC gains could be classified as 'good' anthropometric response as they fell within previously reported gains for similar programmes considered successful. However, the results suggest that the shift to the unique dose of 500 kcal/day during the MAM phase reduced the rate of weight and MUAC gains.

For a noninferiority trial, it is recommended to confirm that the active control had performed as it could have been expected based on past experiences. In our case, we can confirm that this condition was met. Indeed, the recovery rate of the STD group met the minimum SPHERE standards and is among the higher rates reported in the literature for similar programmes that range from below 50% to above 90% (Bailey et al., 2020; Bitew et al., 2020; Desyibelew et al., 2020; Hitchings et al., 2022; Kangas et al., 2019; Mangal & Sivaraman, 2020; UNICEF, 2021). The weight gain velocity of the STD group also met the minimum SPHERE standard of ≥5 g/kg/day which indicates that the programme was of good quality as usually observed figures in IMAM programmatic and even research contexts are below this minimum and rate as low as 2.4 g/kg/day have been reported (Chase et al., 2020; Hendrixson et al., 2020; Trehan et al., 2013). The results of the STD group confirm that the programme operated at a level of quality allowing for a scientifically sound conclusion regarding the experimental MTP model piloted (Kangas et al., 2019).

The recovery rate can be considered as the principal criteria for judging the performance of an IMAM programme and a minimum of 75% has been set as reference (WHO, 2013). Thus, our results showing that the MTP group had a recovery rate above 75% and more importantly was not inferior to that of the STD group with regard to recovery rate, are very encouraging. They clearly indicate that the modified treatment protocol (1000 kcal during the SAM phase and 500 kcal during MAM phase) was as good as the current standard of care. These positive results are in favour of considering the scale up of this MTP model in Afghanistan given the persistent challenges in securing enough resources to accelerate the scale up of acute malnutrition treatment.

The modified daily RUTF dosage is a simplification to standard protocols aimed to ensure maximum coverage of treatment for the most vulnerable children with SAM in resource-constrained contexts. To date, several strategies of modified RUTF daily dosage have been proposed and trialled (UNICEF, 2021). The strategy used in this pilot

TABLE 2 Distribution of children per standard daily dosage of ready-to-use therapeutic food (RUTF) category and level of dose reduction according to the phase of treatment.

		MTP[b] group			
			Dose reduction		
	STD[a] group		SAM[c]	MAM[d]	Total
Standard RUTF dose per day (sachets)[e]	N %	N %	Sachets % STD[f]	Sachets % STD[f]	N %
1.5	0	8	+0.5	−0.5	8
(Weight: 3.5–3.9 kg)	0.00	0.45	+33.3	−33.3	0.39
2	45	147	0	−1.0	192
(Weight[g]: 4.0–4.9 kg)	16.73	8.29	0.0	−50.0	9.40
2.5	210	1,142	−0.5	−1.5	1,352
(Weight: 5.0–6.9 kg)	78.07	64.41	−20.0	−60.0	66.21
3	14	390	−1.0	−2.5	404
(Weight: 7.0–8.4 kg)	5.20	22.00	−33.3	−66.7	19.78
3.5	0	55	−1.5	−3.0	55
(Weight: 8.5–9.4 kg)	0.00	3.10	−42.9	−72.5	2.69
4	0	13	−2.0	−3.5	13
(Weight: 9.5–10.4 kg)	0.00	0.73	−50.0	−75.0	0.64
4.5	0	9	−2.5	−4.0	9
(Weight: 10.5–11.9 kg)	0.00	0.51	−56.6	−77.8	0.44
5	0	9	−3.0	−4.5	9
(Weight: ≥12 kg)	0.00	0.51	−60.0	−80.0	0.44
Total	269	1773			2042
	100.00	100.00			100.0

[a]Standard treatment protocol group/standard daily dose of RUTF.
[b]Modified treatment protocol/reduced daily dose of RUTF.
[c]Treatment phase while the child is severely wasted.
[d]Treatment phase after fulfilling moderate wasting case definition.
[e]Standard RUTF daily dose per the national Integrated Management of Acute Malnutrition guidelines.
[f]Percentage of the standard dose for the body weight category.
[g]Child body weight.

TABLE 3 Nutrition treatment outcomes per analysis approach.

Nutrition outcome	All children	STD protocol	MTP protocol	Reference
Intention-to-treat analysis (n)	2042	269	1773	
Recovered *n* (%)	1703 (83.4)	203 (75.5)	1500 (84.6)	≥75
Defaulted *n* (%)	123 (6.0)	39 (14.5)	84 (4.7)	<15
Died *n* (%)	3 (0.1)	0 (0.0)	3 (0.2)	<10
Nonrecovered (%)	97 (4.8)	21 (7.8)	76 (4.3)	<2
Inpatient transfer (%)	29 (1.4)	1 (0.4)	28 (1.6)	–
Unknown (%)	87 (4.3)	5 (1.9)	82 (4.6)	–
Per protocol analysis	1832	225	1607	
Recovered (%)	1703 (93.0)	203 (90.2)	1500 (93.3)	≥75
Died (%)	3 (0.2)	0 (0.0)	3 (0.2)	<10
Noncured (%)	97 (5.3)	21 (9.3)	76 (4.7)	<2
Inpatient transfer (%)	29 (1.6)	1 (0.4)	28 (1.7)	–

Abbreviations: MTP, modified treatment protocol; STD, standard treatment protocol.

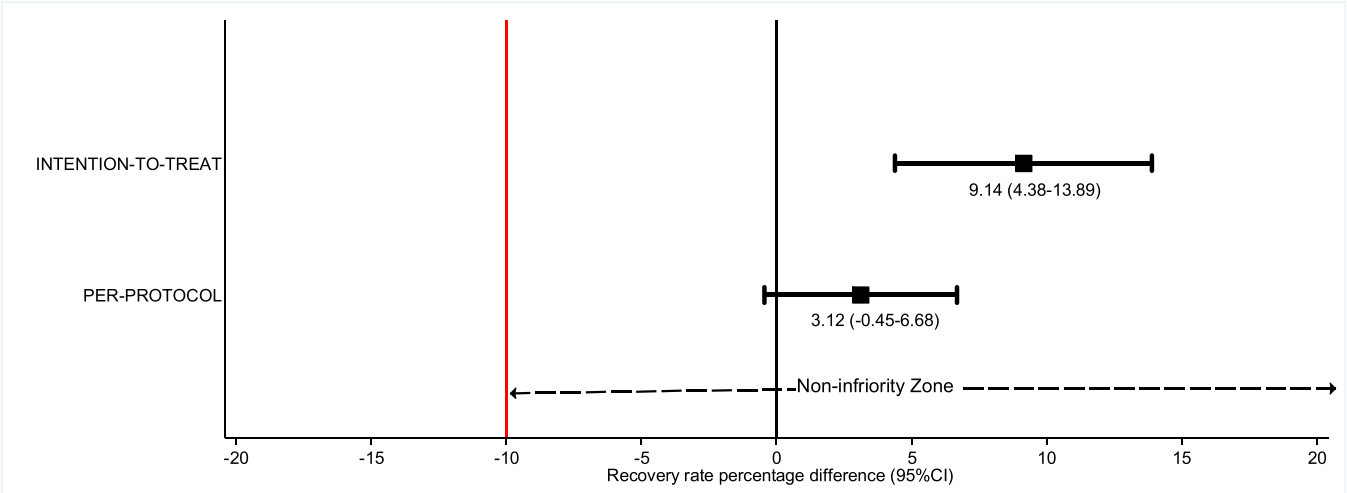

FIGURE 2 Noninferiority graph of the comparison of recovery rates. CI, confidence interval.

programme is similar to that of the Combined Protocol for Acute Malnutrition Study (ComPAS) study, which includes a unique dose of 1000 Kcal/day during the SAM phase and an unique dose of 500 Kcal/day during the MAM phase (Bailey et al., 2018; Bailey et al., 2020). The results of the Per Protocol analysis that included only children who completed the ComPAS study encouraged the continuation of research and justified the implementation of the pilot programme we have analyzed in this paper and supports the conclusion of noninferiority of a modified dosage, including the ComPAS RUTF dosage strategy (Bailey et al., 2020; Mo et al., 2020; Schumi & Wittes, 2011). Another reported recovery rate of a simplified protocol study, which included the ComPAS RUTF dosage strategy, was from a single-arm operational programme implemented in Mali, which reported a 94% recovery rate (UNICEF, 2021). However, the absence of a comparison with the standard weight-based dosage lowered the quality of the evidence, though with a such high recovery rate, it is likely that the noninferiority could have been confirmed (UNICEF, 2021).

The comparison of the recovery rate observed in our study to that of studies that used other modified RUTF dosage strategies also yielded encouraging results (UNICEF, 2021). The recovery rate we observed was higher than what was observed by Kangas et al. in Burkina Faso with the gradual reduction of the RUTF dose according to admission weight of 52.7% for the reduced dosage group versus 55.4% for the standard dosage group (Kangas et al., 2019). It was also higher than the recovery rates observed by the different OptiMA studies of 57.6% and 70.4% (Daures et al., 2020; UNICEF, 2021). The recovery rate we observed was of the same magnitude (90.2%) as the rate observed in a modified RUTF dosage study conducted in Myanmar in which quality of

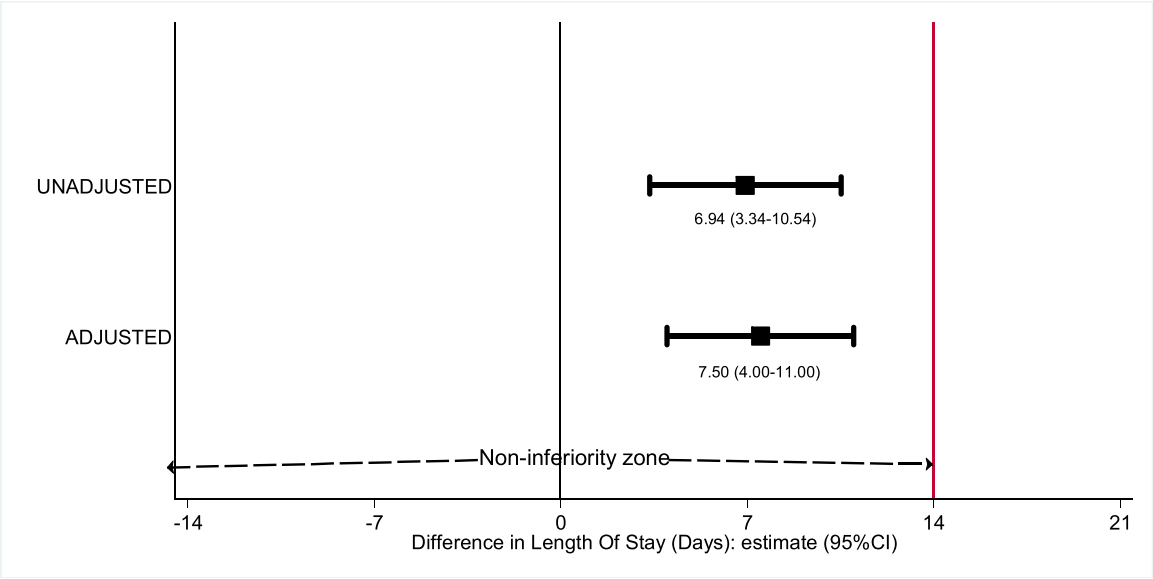

FIGURE 3 Difference in the length of stay: noninferiority analysis. CI, confidence interval.

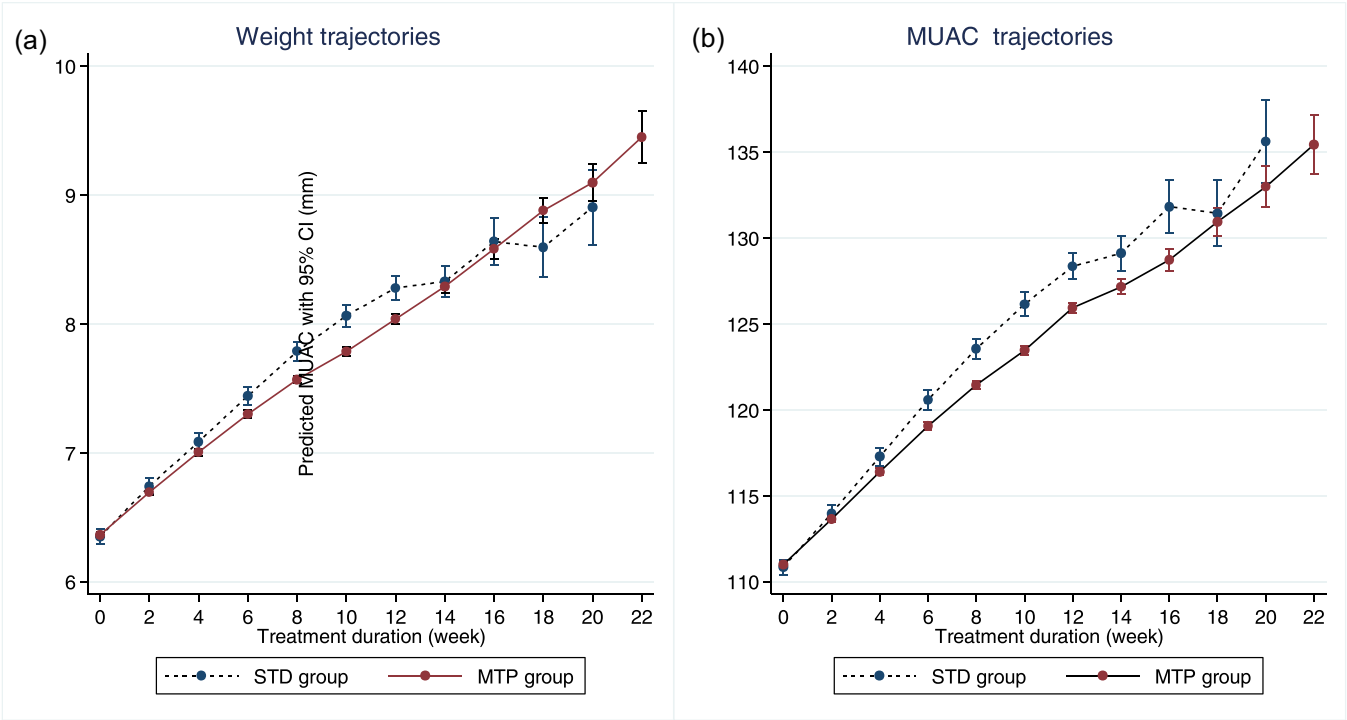

FIGURE 4 (a, b) Weight and mid-upper arm circumference (MUAC) trajectories according to treatment group. MTP, modified treatment protocol; STD, standard treatment protocol.

service delivery was improved through refresher trainings of health workers and community volunteers; strengthened support for caregivers by the establishment of daycare centres; group and individual counselling on feeding practices and close follow up of children with suboptimal response (James et al., 2015). The above advocates in favour of promoting the use of the reduced RUTF dosage strategy piloted in our study.

Another important finding of our study is the confirmation of the noninferiority of the MTP group in comparison to the STD group with regard to LOS. This confirmation of the noninferiority suggests that it might be possible to make savings of RUTF by utilizing the reduced RUTF dosage strategy applied in this study and ultimately improve the country's SAM treatment coverage, a national and global priority.

Data are lacking for the comparison of the observed LOS with previous country experiences. The longer LOS observed can be compared with LOS reported in other countries that tested the reduced RUTF dosage. The three studies identified in the literature reported an average LOS shorter than what we observed in our study varying between 42 and 65 days. We strongly believe that the longer LOS in our study is not related to the MTP protocols, and is more likely due to context-specific factors (Bailey et al., 2020; James et al., 2015; Kangas et al., 2019). Indeed, the Myanmar study reported an average of 42 days under the standard dosage until the MAM phase (James et al., 2015) and the Burkina Faso study, observed an average LOS of around 65 days, under a protocol that treated children with a standard dose during the first 2 weeks and had a lower dose reduction in younger children (Kangas et al., 2019), and the third study mentioned applied the same reduced RUTF dosage strategy as in our study and observed an average LOS of 56 days (Bailey et al., 2020). The most plausible explanation in our study is the low adherence to the follow-up visits, based on visit records, as only 10.9% of the children who recovered strictly adhered to follow-up visit protocols, thereby receiving RUTF PP schedule. It is worth noting that with the introduction of programming adaptations due to COVID-19, there was a mix of different follow-up schedules, ranging from weekly to fortnightly, thereby introducing another factor that may affect the LOS. Data on morbidity during treatment were not available, but this is another factor to explore in future studies.

The weight velocity observed in both groups was within the range of what is usually reported for IMAM programmes, suggesting that both the MTP and STD had acceptable anthropometric responses to treatment (Chase et al., 2020; Hendrixson et al., 2020; Trehan et al., 2013). It was also within the range reported by previous studies that assessed the effect of the different reduced RUTF dosage strategies that observed a weighted velocity varying from 1.9 to 4 g/kg/day (Bailey et al., 2020; James et al., 2015; Kangas et al., 2019). Thus, despite the difference observed between the MTP and the STD groups, there is no reason to be concerned by the observed weight and even MUAC velocities of the MTP group. Indeed, to date, only one study comparing a reduced RUTF dosage to standard RUTF dosage has confirmed noninferiority in terms of weight gain velocity; however, that study used a 90% CI for the interpretation instead of the conventional 95% CI (Kangas et al., 2019). That study also had a tighter margin of noninferiority of −0.5 g/kg/day and observed that the rate of weight gain reduced after the initiation of a reduced dosage phase indicating, similarly to our study, that in general families of children receiving a reduced RUTF dosage struggle to qualitatively replace RUTF. This finding advocates for the combination of the dose reduction simplification with a strengthened infant and young child feeding counselling of caregivers and other prevention interventions throughout the treatment period with intensification once the child has reached the MAM phase. Such counselling added to the sensitization on the adherence to the follow-up visit schedule may contribute to both improving growth velocities and reducing LOS.

When children with SAM are treated only as an inpatient from admission to cure, as in the pre-CMAM standard facility-based model, it is important to have very high weight velocity to accelerate recovery and minimize risk of nosocomial infections. With outpatient management, the risk of nosocomial infection is limited leading experts to relax on weight velocity indicators and propose lower quality threshold of as low as 3 g/kg/day (Ashworth, 2006; Kangas et al., 2019). There have also been concerns that slow weight gain during recovery from SAM will be associated with excess fat synthesis, however comparison of body composition at recovery has in contrary shown that this was not the case (Bahwere et al., 2016; Kangas et al., 2020). Thus, the above indicates that results of weight gain velocity should always be interpreted taking into account the other indicators of response to treatment and programme performance.

This finding is consistent with findings of most recent studies that evaluated this research question and contribute to strengthening the evidence base by adding an experience from a context other than Africa and from real-world programming (Bailey et al., 2020; Cazes et al., 2020, 2021; Daures et al., 2020; Daures et al., 2022; James et al., 2015; Kangas et al., 2019; UNICEF, 2021). To our knowledge, this is the first study to report findings on the reduced daily RUTF dosage from a government run programme in South Asia. In the published literature, there is only one study that reported findings on this topic from an Asian country, but this was for an international nongovernmental organization supported programme (James et al., 2015). Such support usually strengthens the supervision and the quality of services delivery which can explain the higher recovery rate observed in that study compared to what we observed (James et al., 2015).

4.1 | Challenges and limitations

The findings of the present study have been interpreted taking into account its strengths and limitations. The major strengths are the real-world nature of the experiment that enhance the generalizability of the findings, the prospective design of the data collection that improved accuracy and minimized occurrence of files loss, the long data collection period which means that all the phases of the maturation of new intervention were covered, and the coverage of five provinces ensuring a good representativeness of the various Afghan socioeconomic contexts.

The limitations include the fact that the two different protocols were not implemented concurrently, but sequentially, which results in bias such us selection bias and performance bias being inherent in this design; the very short period of data collection for the control group and hence the small sample size; the collection of the data for children prescribed the body weight-based daily dosage in one province only; and the sample size unbalance with one protocol group representing the two third of the total sample analyzed. Another limitation is the fact that most of the children included in the sample were admitted by the MUAC

criterion only, thus the results may not be generalizable to settings with a high proportion of children with WHZ < −3 or a high proportion of nutritional oedema.

Demonstration of positive effects of a nonweight-based daily dosage on effectiveness, treatment coverage and cost-effectiveness is needed to comprehensively inform policy makers on the benefit of the approach and the impact it can have in terms of improving the nutrition and health of children (Sophie Woodhead & Zagre, 2019; UNICEF, 2021; WHO, FAO, UNHCR, UNICEF, & WFP, 2020). This paper provides evidence on the effectiveness of nonweight-based daily RUTF dosage in term of nutrition outcomes, but per the study design no data for cost-effectiveness and treatment coverage analyses were collected. In a separate paper, we will provide information on the effectiveness of this modified dosage combined with reduced frequency of follow-up visits in terms of nutritional outcomes and RUTF total consumption; however, based on available data this information is not sufficient to comprehensively confirm positive effects on costs of SAM treatment and treatment coverage. Thus, further research is needed to confirm that in the Afghanistan context, this simplification contributes to achieving the objectives of reducing treatment costs and expanding treatment coverage. Further research is also needed to confirm that the reduced RUTF daily dosage is associated with similar postdischarge outcomes, including relapse rate and serious disease events when compared to the standard weight-based RUTF daily dosage. Existing evidence from studies conducted elsewhere suggest an improved cost-effectiveness and no adverse postdischarge effects (Bailey et al., 2020; Lelijveld et al., 2021).

5 | CONCLUSION

In conclusion, this experience complements existing evidence on the effectiveness of a modified dosage during times of resource constraints and provides valuable information for the continued implementation of the MTP in Afghanistan. This study contributes to the body of evidence that supports the reflection of a nonweight-based daily RUTF dosage in national and global policies and guidelines to improve coverage of all children in need of treatment. Furthermore, we recommend additional studies with a strong research design and in a variety of settings to inform operational and costing gaps that remain on the use of this modified dosage protocol.

AUTHOR CONTRIBUTIONS

Paluku Bahwere and Grace Funnell conceptualized and designed the study analysis. Paluku Bahwere developed the analysis plan and led the analysis. Wilfred Bengnwi conducted an initial analysis of programmatic data. Paluku Bahwere and Grace Funnell led the writing of the manuscript. Ahmad Nawid Qarizada, Sophie Woodhead, and Minh Tram Le provided critical feedback and inputs on the drafts of this manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Afghanistan Ministry of Public Health (MoPH). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of Afghanistan MoPH.

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