

Effect of a multi-nutrient fortified supplement on immunity in Indian Children: A randomized controlled trial

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Abstract

An open label, two arm, matched pair, cluster randomized controlled trial was conducted to assess the impact of a multi-nutrient Fortified Malt-Based Food (FMBF) on immunity outcomes in Indian school going children (7-10 years). Participants (n=445) in test group schools received FMBF (27g in 150 mL lukewarm water) twice daily for 9 months along with dietary counselling (FMBF+DC); participants (n=462) in control group schools were provided DC alone. Study design and baseline data were published previously. This paper reports primary and secondary outcomes assessed at 3, 6, and 9 months. Primary outcomes included number of ill days due to gastrointestinal infections (GI) and acute respiratory infections (ARI). Secondary outcomes were frequency and severity of GI and ARI episodes, and school absenteeism related to these illnesses over the intervention period. The test group participants fell ill for 6 days (SE 0.234) lesser than the control group ($p<0.001$). Participants in the test group had less illness episodes/month ($p<0.001$), had overall less severity episodes for GI ($p=0.0030$) and ARI ($p=0.0005$) and were less absent from school at 9 months versus control group ($p=0.001$). The improvements in immunity outcomes became evident from 3 months itself and continued at 6 and 9 months of intervention. Significant improvements in serum vitamin B12 ($p=0.017$), vitamin E ($p<0.001$), and selenium ($p=0.016$) were observed in the test group. In conclusion, nine months of FMBF supplementation alongside dietary counselling significantly improved immunity outcomes, reduced GI and ARI-related morbidity, decreased school absenteeism, and enhanced micronutrient status compared with dietary counselling alone.

Keywords: Immunity; Fortified Malt-Based Food; Gastrointestinal infection; Acute Respiratory infection; School absenteeism; Children; Multi-nutrient supplement

1. Introduction

Low- and middle-income countries (LMIC), including India are currently facing a triple burden of malnutrition, that encompasses undernutrition, overnutrition and micronutrient deficiencies. Globally, half of the childhood deaths are due to undernutrition (1-4). The mortality risk of children between 5-14 years of age was estimated to be 7.5 deaths per 1000 children in 2016 (5) which reduced to 3 per 1000 in 2021 (6). It has been observed that in the last two decades the mortality rates of under 5 years (4.0%) has decreased faster than the mortality rate in children aged 5-14 years (2.7%). Globally, the highest incidence in 2021 (across ages and sexes) were upper respiratory infections (12.8 billion), and diarrheal diseases (4.67 billion) (4). Although, the highest incidence rates of URIs were in children younger than two years, the largest number of episodes were observed in children aged 5-9 years (7). In India, 0.65% of total DALYs were contributed by URI and 6.92% of DALYs were due to diarrhoea in 5-9 year old children (4).

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National representative data from the Comprehensive National Nutrition Survey (CNNS, 2019) (8), for Indian children aged 5-9 years reported that nearly one-fourth of the children were stunted, a similar percentage of children (24.8 %) had low BMI, and 35% were underweight, with 10% severely underweight. Individual studies from various parts of the country, have also shown that stunting among school going children ranged from 13.8 % to 56.1 %, wasting ranged from 6.7% to 75% and underweight ranged from 6.6% to 83% (9). These could be attributed to various risk factors including socio-economic status, geographic location, dietary habits and intake, infections and the educational status of parents (10). The school-going age (7-11 years) is a crucial period when the body accumulates nutrients essential for growth during adolescence. This stage is vital for developing a strong immune system, overall health, and enhance cognitive development and laying the foundation for the second growth spurt during adolescence.

While the concept of the 'first 1000 days' of a child's life from conception until 2 years of age has gained much recognition and been addressed worldwide, it is equally imperative to realise the potential for developing age-specific interventions through childhood and adolescence. Children in middle childhood, or those aged 5-9 years, are more likely to be susceptible to infections and malnutrition as compared to older children—key constraints to their growth and development.

Immune dysfunction is both cause and consequence of malnutrition (11-13). Various nutrients play a significant role in maintaining the immune system in the human body by supporting the structural and functional integrity of mucosal cells, differentiation, proliferation and functioning and movement of innate cells, antimicrobial effects, reduction of inflammation, antioxidant and antimicrobial effects, working either alone or in synergy (14). Micronutrient supplementation in school children has been associated with decreased incidence of diarrhoea and fever (15), along with reduced duration of general symptoms of respiratory and gastrointestinal infections (16). In addition to hindering physical growth, repeated episodes of illness can lead to school absenteeism, which may subsequently have a negative impact on cognitive development.

Micronutrient deficiencies like, those of folic acid, vitamin B12, vitamin D, iron, and zinc are associated with impaired growth, weakened immunity, recurrent infections and diseases and impaired cognitive development (17-19). According to the CNNS India data 2018, 28% school going children had folate deficiency, 24% were anemic, 22% had Vitamin A deficiency, 18% had Vitamin D deficiency, 17% had zinc deficiency, 17% had iron deficiency, and similar percentage had low serum ferritin levels (8). A recent study on 600 school going children in the eastern state(s) of India reported that 49% children had anemia, 18% had corneal and conjunctival xerosis (19). Another multicentric study in India reported that 69.2 % of the school going children (6-16 years) have more than two micronutrient deficiencies (20). Research has shown that micronutrient supplementation in the form of fortified drink or biscuits reduced anemia and improved iron status among school going children. Additionally, other studies reported improvement in vitamin B2, B12, D and folic acid on consumption of micronutrient fortified foods in school going children (21-24) .

The impact of multiple micronutrient-fortified foods on child growth and development is well supported by existing evidence (25-28). However, to the best of our knowledge, no comprehensive study has been conducted in India to assess the impact of multi-nutrient fortified malt-based food on immunity outcomes among school going children. The present study aimed to assess the impact of fortified malt-based food (FMBF) combined with dietary counselling, compared to dietary counselling alone, on immunity and related health outcomes in school-aged children (7–10 years). The primary objective was to evaluate the effect of the intervention on the number of ill days due to gastrointestinal and respiratory infections over a 9-month period. Secondary objectives included assessing frequency, severity, and school absenteeism related to these illnesses, as well as changes in gut integrity, mucosal immunity, and biochemical nutritional status.

2. Materials and Methods

An open-label, 2-arm, parallel-group, matched-pair cluster RCT, in participants aged ≥ 7 to ≤ 10 years old with height-for-age z scores (HAZ) of ≥ -3 to ≤ -1 and in good general health was conducted from July 2017 to July 2018, at multiple sites in Pune, India (29). The study was executed in accordance with the protocol (Clinical Study Protocol 204477, version 5.0, dated 10Oct2017), International Council on Harmonization Guidelines for Good clinical practices and the Declaration of Helsinki (Clinicaltrial.gov, NCT02542865) and the Indian Council of Medical Research ethical guidelines. The study was registered at ClinicalTrials.gov with registration number NCT02542865; available at <https://clinicaltrials.gov/study/NCT02542865> . Prior to the initiation of the study, the protocol and all subsequent amendments were approved by an independent institutional ethics committee of Jehangir Clinical Development Centre Pvt Ltd., Pune, India (ECR/352/Inst/ MW2013). Written informed consent was obtained from one of the parents or legally accepted representatives (LAR) of each participant and written assent was secured from all participants prior to the commencement of any study-specific procedures. Participants were allowed to withdraw from the study at any time

at their own request. Detailed study design has been published previously (29). In this paper, we present the results on the primary and secondary outcomes.

The primary outcomes of the study were to determine the total number of ill days due to most common paediatric illnesses viz., gastrointestinal infection (GI) and acute respiratory infection (ARI) in the participants receiving FMBF (test product) with dietary counselling in comparison to the participants receiving dietary counselling alone over a period of 9 months. The secondary outcomes included immune function measures like assessment of frequency and severity of the GI and ARI episodes, school absenteeism due to these episodes, change from baseline in the gut integrity as measured by lactulose: mannitol test and urinary neopterin test, change from baseline in mucosal immunity. Additionally, serum micronutrients levels (vitamins A, B12, D, E, iron, folate, and trace elements Zn, Fe, copper, selenium), macronutrient intake status and Individual dietary diversity score (IDDS) (30) were assessed to ascertain nutritional status and to adjust for confounding due to differential dietary intake of the participants. Immunity/inflammatory markers like C-Reactive Protein (CRP), Alpha 1-Acid Glycoprotein (AGP) and Iron status markers e.g. Serum Transferrin Receptor (sTfR), and Serum ferritin were also assessed.

2.1. Study Interventions

Four co-educational schools with no history of outbreaks of any infectious disease cases in past one month, consented to participate in this study. These schools were matched based on size (number of participants aged 7 to 10 years), socioeconomic profile, and type of school (government-subsidized or private) and a total of 924 children of either sex completed the study. According to the randomization schedule, schools within each matched pair were randomly allocated to one of two intervention groups: (1) the test group, which received a multi-nutrient FMBF (Fortified Malt-Based Food) along with dietary counselling, or (2) the control group, which received only dietary counselling. After collecting baseline data, a total of eight visits (visit 3 to visit 10) were conducted to collect follow-up data for intervention as presented in Figure 1.

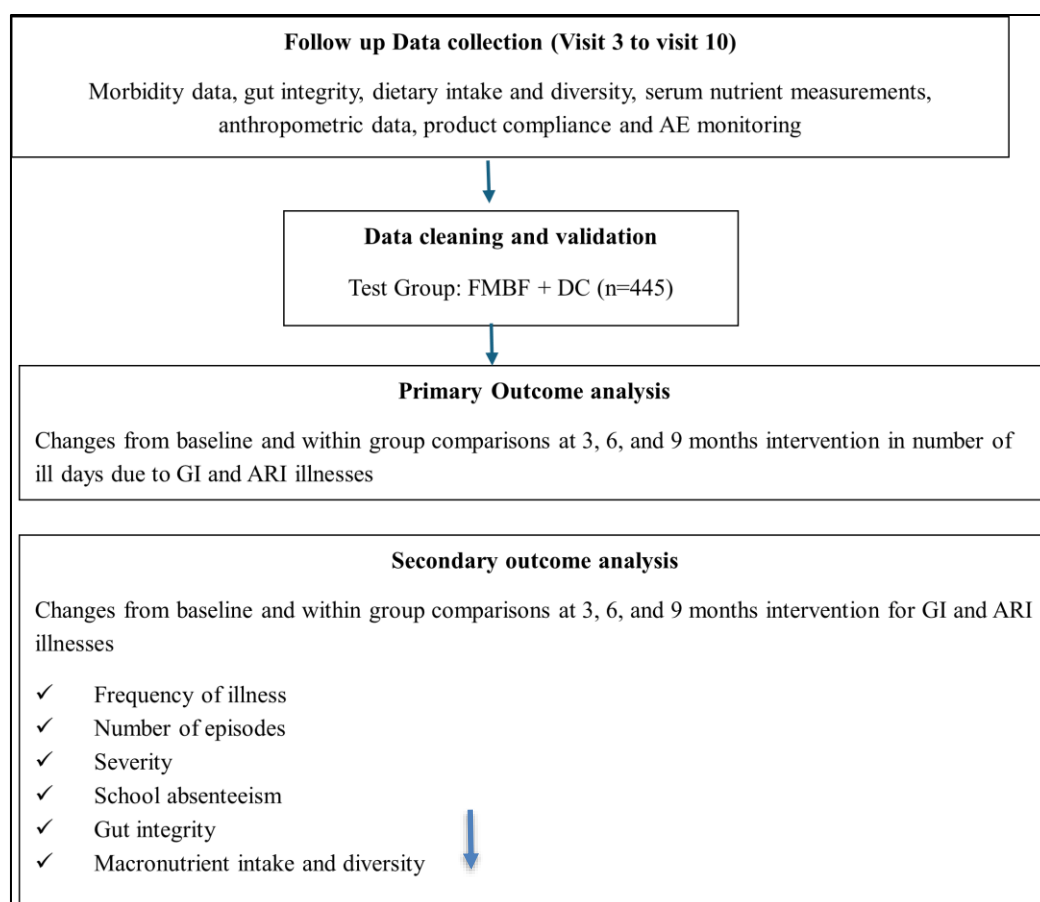


Figure 1 Follow up plan for study intervention on immunity outcomes

All the study participants in the test arm (n=462) were provided the FMBF supplement (27 g in 150 mL lukewarm water) to be consumed twice daily for 9 months. A 9-month period was chosen to ensure adequate biological “wash-in,” to capture multiple infection seasons, accrue sufficient events for a cluster design, and maintain operational feasibility within the school calendar—maximizing the likelihood of detecting true differences in illness burden while minimizing avoidable biases (31-33). All participants and study personnel were blinded to treatment allocation during randomization and blinded data review, with access to treatment codes strictly restricted.

The Fortified Malt based Food is a multi-nutrient supplement designed to support nutritional needs of children. The test product provided 203.6 kcal energy, 1.1 g fat, 5.9 g protein, and 42.7 g carbohydrates per 54 g (two servings per day) along with 12 vitamins and 11 minerals. Detailed nutrient composition is described in **Supplementary Table 1**.

2.2. Data Collection

Data for primary and secondary outcomes due to GI and ARI illnesses were collected in each visit and recorded on diagnosis form and were analysed by study physicians. Data on demography, medical history, and hemoglobin (Hb) (using Pronto) were measured and recorded at baseline (Visit 1). Anthropometric measurements, general physical examination, and vital signs were assessed at baseline (Visit 1) and at the end of the study (Visit 10). Blood samples for serum micronutrients, gut integrity and inflammatory markers were collected and analysed for all the participants at baseline (Visit 2) and the end of the study (Visit 10) were collected. Dietary intake data at baseline and end of the study were obtained using 24-hour recall method and was used to calculate Individual Dietary Diversity Score (IDDS)³¹ and nutrient intake of participants. Details of data collection and assessment methods were presented in our paper published previously (29).

Adverse events (AEs) were observed and recorded from Visit 3 to Visit 10 in addition to those reported by participants/parents/LARs to study physicians, on an ‘as and when’ basis or through weekly symptom checklists.

2.3. Data analysis

Descriptive statistics were used for demography, baseline characteristics, safety assessment (including laboratory tests) using n [%] for categorical measurements and, mean, standard deviation [SD] / standard error (SE), minimum, and maximum for continuous measurements. Data for primary and secondary outcomes was analysed for modified intention to treat (mITT) population and have been presented in this manuscript. The mITT population was defined as all participants in the safety population with any post-interventional assessment (SPWR) who completed the entire intervention phase and attended the end-of-study visit (29).

The number of ill days due to GI and ARI episodes over 9 months and the number of school absenteeism days were analysed using zero-inflated Poisson models with study group, gender and baseline IDDS as covariates. The monthly frequency of GI and ARI episodes was analysed using an ANCOVA model with study group, gender, and baseline IDDS as covariates, that was repeated at 3, 6, and 9 months separately for each disease episodes. The changes in IDDS, dietary intake and biochemical micronutrient levels from baseline at 9 months was analysed using ANCOVA model with study group, gender and baseline value as covariates. Fisher’s exact test and Odds ratio (OR) was used to compare frequency of severity (mild, moderate, severe) of GI or ARI episodes between the two groups. Adjusted means for each study group, 95% confidence intervals, within-group p-values, difference between the study groups, 95% confidence intervals of the difference, and the between-group p-values were also presented based on the above statistical models. All statistical tests of hypotheses were two-sided and employed a level of significance of $\alpha=0.05$.

3. Results

3.1. Demographic and baseline characteristics

A total of 924 participants from four schools were enrolled in the two groups (test: n=462; control: n=462). Of these, 907 participants completed the study (test: n=445; control: n=460). CONSORT diagram and baseline characteristics in detail have been published previously (29).

3.2. Immunity outcomes

3.2.1. Number of ill days

The primary objective of the study was to evaluate the total number of ill days due to GI and/or ARI over a 9-months intervention period. The mITT analysis revealed that number of ill days were significantly lower for test group at

2.3 days (SE 0.2479) as compared to 8.3 days (SE 0.3845) in control group at 9 months ($p < 0.001$) (**Figure 2**). Thus, the participants in test group were 6 (SE 0.234) days less ill as compared to control group ($p < 0.001$) at 9 months due to GI and/or ARI illnesses. Time-point analyses revealed that the reduction in ill days was evident as early as 3 months post consumption, with participants in the test group experiencing 0.9 (SE 0.1509) ill days compared to 3.9 (SE 0.3007) ill days in the control group ($p < 0.001$). At 6 months, the participants in test group were 6 (SE 0.230) days less ill as compared to participants in the control group ($p < 0.001$), that continued at 9 months. Relative to the control group, the test group had 76% fewer ill days at 3 months, 75% fewer at 6 months, and 72% fewer at 9 months.

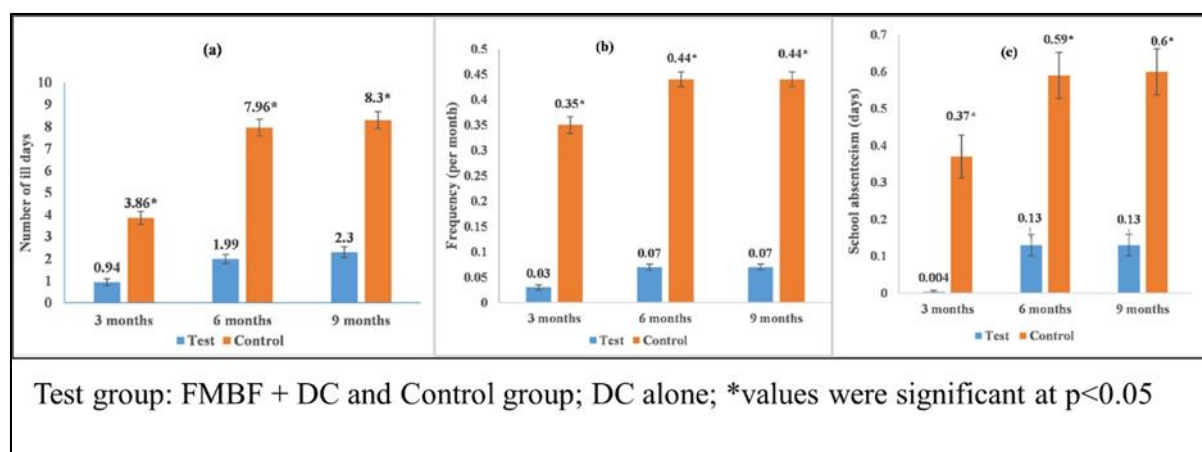


Figure 2 Comparison of immunity outcomes [a. Number of ill days; b. Frequency (per month); c. School absenteeism (in days)] among participants due to GI and/or ARI in test and control groups

When analysed separately for GI and ARI (**Supplementary Table 2**), a significant reduction in number of ill days due to ARI were observed in test group participants [0.9 (SE 0.146) ill days] as compared to control group participants [3.4 (SE 0.2839) ill days] at 3 months ($p < 0.001$), with reductions persisting at 6 and 9 months (both $p < 0.001$). GI-related ill days showed a similar trend: 0.6 (SE 0.12) vs. 1.9 (SE 0.20) at 3 months ($p < 0.001$), with sustained differences at 6 and 9 months (both $p < 0.001$). (**Supplementary Table 2**).

3.2.2. Frequency of illness

At 9 months, mean monthly frequency was 0.07 (SE 0.006) episodes in the test group compared with 0.44 (SE 0.015) episodes in the control group ($p < 0.001$). Similar differences were observed at earlier timepoints. At 3 months, frequencies were 0.03 (SE 0.005) vs. 0.35 (SE 0.017) episodes/month ($p < 0.001$), and at 6 months 0.07 (SE 0.006) vs. 0.44 (SE 0.015) episodes/month ($p < 0.001$) (**Figure 2**). These reductions were consistent for both GI and ARI illnesses across all three timepoints; (**Supplementary Table 2**).

3.2.3. Episodes of illness

A higher proportion of participants in the test group reported no episodes of GI and/or ARI compared with the control group at 3 months (83.1% vs. 36.1%), and this difference was sustained at 6 and 9 months of intervention (**Table 1**). At 3 months, the odds of experiencing ARI were significantly lower in the test group compared with controls (OR = 0.126, 95% CI: 0.090–0.175, $p < 0.001$), corresponding to approximately an eight-fold higher likelihood of remaining ARI-free. A similar effect was observed for GI, with an OR of 0.127 (95% CI: 0.060–0.245, $p < 0.001$). The protective effect of the intervention was evident as early as 3 months and persisted through 6 and 9 months (**Table 1**).

Table 1 Odds ratio of number of episodes GI and ARI at 3, 6 and 9 months of intervention of FMBF supplementation + DC (test group) and DC alone (Control group)

Illness	Test (%)	Control (%)	OR (95% CI)	p-value
GI				
3 months	11 (2.5)	77 (16.7)	0.127, (0.060, 0.245)	< 0.001*
6 months	37 (8.3)	170 (36.8)	0.156, (0.103, 0.232)	< 0.001*

9 months	43 (9.7)	183 (39.6)	0.163, (0.110, 0.238)	< 0.001*
ARI				
3 months	67 (15.1)	270 (58.4)	0.126, (0.090, 0.175)	< 0.001*
6 months	139 (31.2)	382 (82.7)	0.095, (0.069, 0.132)	< 0.001*
9 months	159 (35.7)	390 (84.4)	0.103, (0.074, 0.143)	< 0.001*
GI and/or ARI				
3 months	75 (16.9)	295 (63.9)	0.115, (0.083, 0.158)	< 0.001*
6 months	163 (36.6)	415 (89.8)	0.066, (0.045, 0.095)	< 0.001*
9 months	184 (41.3)	421 (91.1)	0.069, (0.046, 0.101)	< 0.001*
Values are number (percentages) of participants in test and control group with illnesses at 3, 6 and 9 months of intervention. OR= Odds Ratio, CI= Confidence Interval, Test group: FMBF + DC and Control group; DC alone				
*Values were significant at $p < 0.05$ between the test and control group				

3.2.4. Severity of illness

As shown in **Figure 3**, the distribution of illness severity differed between groups. A significantly lower proportion of participants in the test group reported mild or moderate episodes of GI and ARI compared with controls. Statistically significant differences were observed for GI ($p=0.003$), diarrhea ($p=0.037$), vomiting ($p=0.009$), and ARI ($p<0.001$) versus control group. No severe GI episodes were reported in either group. Severe ARI episodes were very low and had no significant differences between groups. Detailed percentages for each severity category are presented in **Figure 3**.

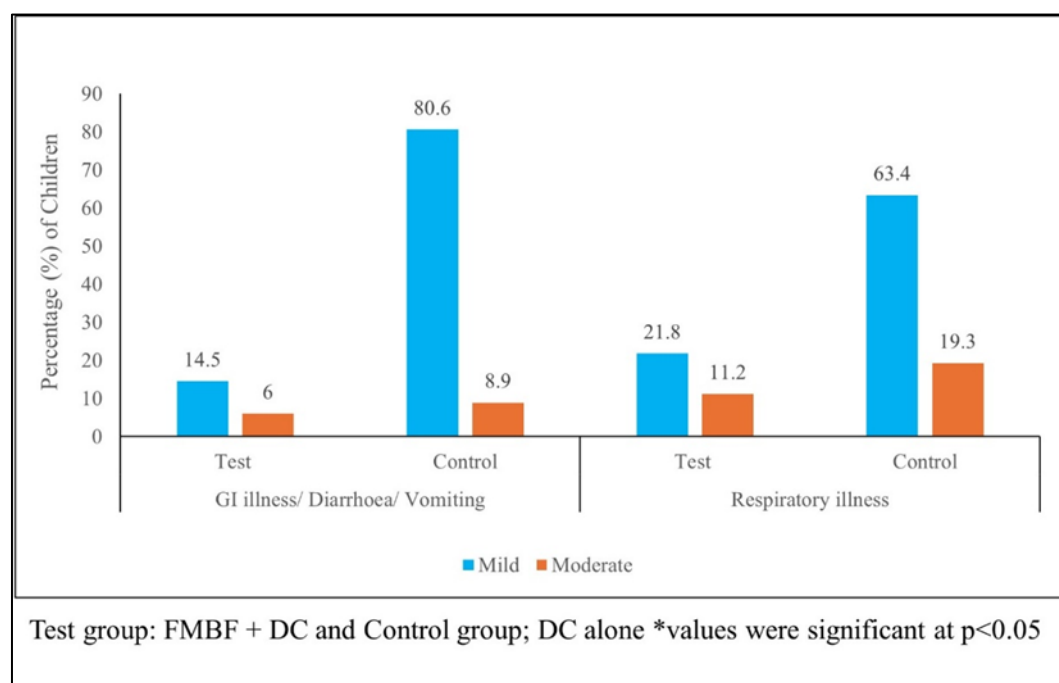


Figure 3 Comparison of percentage of participants with mild and moderate illness in Test and Control group at 9 months

3.2.5. School absenteeism

At 9 months, participants in the test group missed significantly fewer school days due to GI and/or ARI compared with controls, with a mean reduction of 0.48 days per child (SE 0.061, $p < 0.001$; **Figure 2**). This represented an ~82% lower number of absent days relative to the control group. A significant effect was evident as early as 3 months,

with a mean reduction of 0.37 days (SE 0.055, $p<0.001$; ~78% lower than controls), increasing to 0.48 days at 6 months (SE 0.061, $p<0.001$). The reduction was sustained through the 9-month intervention period.

3.2.6. Changes in gut integrity

At 9 months, urinary neopterin and salivary IgA levels increased significantly from baseline in both test ($p=0.046$ and $p=0.009$, respectively) and control groups ($p=0.037$ and $p=0.010$, respectively). However, no significant differences were observed between groups for urinary neopterin ($p=0.502$) or salivary IgA ($p=0.573$). Similarly, no significant changes were observed in gut permeability assessed by the lactulose: mannitol ratio within or between groups ($p>0.49$ for all comparisons) (Supplementary **Table 3**).

3.2.7. Changes in biochemical parameters and nutritional status

After 9 months of intervention, both the test and control groups showed significant increases from baseline in mean serum concentrations of most micronutrients, including vitamins A, B12, D, E, folate, zinc, and selenium, except copper or iron (**Table 2**).

Between-group comparisons demonstrated significantly greater increases in the test group compared with the control group for vitamin B12 [mean difference 11.0 (SE 4.6) pg/mL, $p=0.017$], vitamin E [0.041 (SE 0.008) mg/dL, $p<0.001$], and selenium [2.6 (SE 1.07) $\mu\text{g/L}$, $p=0.016$]. For vitamin D, folate, iron, and ferritin, mean concentrations were higher in the test group than in the control group at 9 months, but missed significance (Table 2). There were no significant between-group differences in markers of inflammation, including C-reactive protein (CRP), α 1-acid glycoprotein (AGP), and serum transferrin receptor (sTfR).

The prevalence of deficiencies in vitamin A, vitamin B12, vitamin E, folate, zinc, and iron decreased from baseline in both groups after 9 months of intervention and statistically significant reductions were observed for vitamin B12 and vitamin E (**Supplementary Table 2**).

Table 2 Comparison of changes in IDDS, dietary intake, and biochemical micronutrient levels and immunity markers from baseline and at 9 months, for test (n=445) and control group (n=462)

Parameter	Group	Within group comparison			Between the groups	
		Mean difference from baseline (SE)	95% CI	p-value	Mean difference (SE)	p-value
IDDS	Test	1.4 (0.049)	(1.31, 1.50)	0.1846	1.04 (0.608)	<0.001*
	Control	0.36 (0.048)	(0.27, 0.46)	0.6726		
Energy (Kcal)	Test	94.8 (14.9)	(65.6, 124.0)	0.2831	186 (20.8)	<0.001*
	Control	-91.1 (14.6)	(-119.7, -62.4)	0.2987		
Protein (g)	Test	5.92 (0.547)	(4.84, 6.99)	0.0429	8.26 (0.766)	<0.001*
	Control	-2.34 (0.535)	(-3.39, -1.29)	0.2068		
Carbohydrates (g)	Test	-10.5 (2.16)	(-14.7, -6.3)	0.0419	4.48 (3.02)	0.138
	Control	-15 (2.11)	(-19.1, -10.8)	0.0201		
Fats (g)	Test	14.79 (0.82)	(13.18, 16.40)	0.1976	17.7 (1.16)	<0.001*
	Control	-2.89 (0.803)	(-4.47, -1.31)	0.7217		
Serum Vitamin A, mcg/L	Test	2.6 (0.321)	(1.97, 3.23)	0.0343	-0.27 (0.449)	0.548
	Control	2.87 (0.315)	(2.25, 3.49)	0.0295		
Serum Vitamin B12, pg/mL	Test	54.6 (3.31)	(48.1, 61.1)	0.0118	11 (4.62)	0.017*
	Control	43.6 (3.24)	(37.2, 49.9)	0.0180		
Serum Vitamin D, ng/ml	Test	2.75 (0.21)	(2.34, 3.17)	0.0058	0.517 (0.293)	0.078
	Control	2.24 (0.206)	(1.83, 2.64)	0.0082		

Serum Vitamin E, mg/dL	Test	0.054 (0.005)	(0.043, 0.065)	0.0190	0.041 (0.008)	<0.001*
	Control	0.013 (0.005)	(0.003, 0.024)	0.2464		
Serum Folate, ng/mL	Test	0.68 (0.033)	(0.619, 0.750)	0.0024	0.049 (0.047)	0.29
	Control	0.63 (0.033)	(0.571, 0.699)	0.0027		
Serum Selenium, mcg/L	Test	8.49 (0.77)	(6.98, 10.0)	0.0204	2.59 (1.07)	0.016*
	Control	5.9 (0.75)	(4.42, 7.37)	0.0413		
Serum Zinc, mcg/dL	Test	16.5 (0.89)	(14.8, 18.3)	0.0028	-0.39 (1.24)	0.753
	Control	16.9 (0.87)	(15.2, 18.6)	0.0026		
Serum Copper, mcg/dL	Test	-1.42 (0.817)	(-3.03, 0.18)	0.2733	-0.56 (1.14)	0.625
	Control	-0.87 (0.801)	(-2.44, 0.70)	0.4660		
Serum Iron, mcg/dL	Test	0.37 (0.918)	(-1.43, 2.17)	0.7778	1.04 (1.28)	0.415
	Control	-0.67 (0.899)	(-2.44, 1.09)	0.5987		
Serum ferritin	Test	3.48 (0.605)	(2.29, 4.67)	0.0272	1.65 (0.84)	0.051
	Control	1.83 (0.593)	(0.66, 2.99)	0.0839		
C-Reactive Protein	Test	0.06 (0.009)	(0.04, 0.08)	0.0506	0.01 (0.013)	0.53
	Control	0.05 (0.009)	(0.04, 0.07)	0.0672		
Alpha 1-Acid Glycoprotein	Test	0.16 (0.715)	(-1.25, 1.56)	0.8346	0.57 (0.997)	0.565
	Control	-0.41 (0.701)	(-1.79, 0.96)	0.6202		
Serum Transferrin Receptor	Test	-0.04 (0.013)	(-0.07,-0.02)	0.0852	0.02 (0.018)	0.305
	Control	-0.06 (0.013)	(-0.09,-0.04)	0.0412		

Values are adjusted means and standard error (SE); CI= Confidence Interval, IDDS- Individual Dietary Diversity Score, Test group: FMBF + DC and Control group; DC alone. *Values were significant at p<0.05

3.3. Adverse events and safety

Safety assessments included assessment of adverse events (AEs) and serious adverse events (SAEs) for participants at baseline, and each follow-up visit until the end of study visits. Treatment-related Adverse Events (TRAEs) were reported in only two participants (0.4%) in the test group, specifically one case of pyrexia and one case of upper respiratory tract infection. Consequently, with only 0.4% of participants in the test group (and 0.2% overall) experiencing treatment-related AEs, the absence of treatment-related serious adverse events (SAEs), and no withdrawals due to AEs, the study treatments were generally considered well tolerated.

4. Discussion

The present open label, two-arm, matched pair, cluster randomized controlled trial conducted on mildly undernourished Indian school children (7-10 years) in urban settings was one of the large-scale studies, focussing on the impact of multi-nutrient supplementation on immunity outcomes. At baseline, the present study participants had multiple nutrient inadequacies and 86 % had HAZ score between $\geq -2SD$ and $\leq -1 SD$ (29).

The participants in the test group were 3.0 (SE 0.196) days less likely to fall ill as compared to control group ($p < 0.001$) at 3 months of intervention itself. Further, the number increased to 6 less ill days among test group participants as compared to control groups, that continued at 9 months of intervention. The reduction in illness days observed in our trial is consistent with, and in some cases larger than, effects reported in comparable school-based nutrition interventions. For example, a cluster-randomised trial in Thailand providing micronutrient-fortified seasoning powder for 31 weeks reported a modest reduction in common morbidity episodes and improved cognitive outcomes, though the absolute decline in illness days was smaller than in our study (34). Trials conducted in Indian schoolchildren using fortified malt or cocoa-based beverages have similarly demonstrated improved micronutrient status and functional

outcomes, with secondary analyses noting reductions in self-limiting infections (35, 36). A study in the Philippines using a multi-micronutrient-fortified fruit powder beverage also reported decreased morbidity, including fewer respiratory infections, when delivered over an academic term (37). By contrast, short-duration interventions in largely micronutrient-replete populations, such as fortified breakfast cereal trials in the United States, did not demonstrate significant reductions in illness days (38). This underscores the importance of population context, baseline nutrient insufficiencies, intervention formulation, and duration of exposure. Taken together, our findings are in line with evidence from Asian school-age populations in which fortified food vehicles provided multiple micronutrients; they also extend the literature by demonstrating consistent reductions in both gastrointestinal and respiratory illness burden over a 9-month school year.

In our study, children receiving the fortified malt-based food experienced fewer illness episodes overall, and the odds of remaining free from gastrointestinal and respiratory infections were approximately eight times higher compared with controls at 3 months (**Table 1**). Apparent reductions in the proportion of mild and moderate GI and ARI episodes may also reflect the lower overall frequency of illness in the intervention arm, rather than a true shift in severity distribution. The direction of benefit is consistent with previous school-based fortification trials, though our effect sizes are larger. For example, a Thai cluster trial reported more modest reductions in respiratory illness incidence (RR: 0.83; 95% CI: 0.73–0.94) and diarrhea (RR: 0.38; 95% CI: 0.16–0.90) with fortified seasoning powder (39). A recent meta-analysis similarly reported reduced risk of diarrhea (RR: 0.79) and fever (RR: 0.85), but no significant effect on respiratory infections or vomiting (15). Compared to these studies, the stronger protection observed in our trial may reflect differences in baseline nutritional vulnerability, the specific nutrient composition of the FMBF, and the longer duration of supervised intake (9 months). An Indonesian study of mildly wasted children further supports this interpretation, reporting faster recovery and shorter hospital stays with micronutrient supplementation alongside nutrition education (40).

The reduction in illness-related absenteeism of approximately 0.5 days over nine months, although statistically significant, represents a modest absolute change at the individual level. At baseline, children missed ~4–5 days per year, so an incremental reduction is unlikely to influence individual academic attainment. Comparable small changes in attendance have been reported in other school fortification trials, where gains were typically <1 day per term (37, 41). By contrast, interventions that combined nutritional support with deworming or hygiene promotion have shown more pronounced effects on attendance. For example, a large school-based deworming trial in Kenya reported a 25% reduction in absenteeism, equivalent to 7 additional school days per child annually (42). Similarly, integrated programmes in sub-Saharan Africa and South Asia that coupled micronutrient fortification with WASH (water, sanitation, hygiene) or deworming reported reductions of 2–6 days in annual absenteeism (43). Against this backdrop, the observed 0.5-day reduction in our study, though modest, remains meaningful because it was achieved solely with a food-based intervention rather than combined with disease-control measures. At scale, the cumulative gain could be substantial.

Participants in the test group showed a modest but statistically significant increase in BMI with mean change from baseline to endline being 0.218 kg/m² compared to control group where mean change was 0.054 kg/m² at 9 months. Importantly, these values remained within the normal range according to WHO BMI-for-age standards (44). This suggests that the intervention supported healthier BMI gain without shifting children into overweight categories. The observed increase is consistent with improved nutritional status and may partly reflect reduced illness burden, which can otherwise impair appetite, nutrient absorption, and growth. The FMBF supplement may have a potential role to play in disrupting the cycle of infection and undernutrition through enhancement of immune function in the current study. This improvement may provide a foundation for better nutritional outcomes and catch-up growth during later pubertal development.

The intervention led to significant increases in serum vitamin B12, vitamin E, and selenium in the test group compared with controls. This is consistent with the nutrient profile of the fortified malt-based food (FMBF), which provided substantial amounts of these nutrients relative to daily requirements (46.6% RDA for vitamin B12, 18% RDA for vitamin E, and nearly 100% RDA for selenium per daily serving). This concordance strongly supports the interpretation that the FMBF directly repleted the nutrients it was designed to deliver, and that these improvements likely contributed to the reduced morbidity observed.

Our findings are consistent with a broad body of evidence showing that multi-micronutrient fortification improves biochemical status in school-aged children. For example, studies in Vietnam have demonstrated that fortified biscuits and beverages significantly improved ferritin, zinc, and retinol levels, and reduced anemia and zinc deficiency (23, 41, 45). Similarly, Bangladeshi and Indonesian trials of fortified foods and multiple micronutrient supplements have reported improvements in hemoglobin, serum ferritin, zinc, and vitamin A status (46, 47). In Indian settings, fortified

school lunches and oral nutritional supplements (ONS) have been shown to reduce the prevalence of vitamin A and folate deficiency and improve circulating vitamin B12 and iron biomarkers, while also supporting growth (21, 24, 28, 48). Collectively, these studies reinforce the evidence that school-based fortification and supplementation programs can address multiple micronutrient deficiencies effectively across diverse populations.

The specific nutrients that improved in this trial—vitamin B12, vitamin E, and selenium—have direct and complementary roles in immune defense. Vitamin B12 promotes lymphocyte proliferation, cytokine production, and enhances CD8+ T-cell and natural killer cell activity (49). Vitamin E and selenium provide antioxidant protection to immune cells and regulate inflammatory responses (50, 51). These improvements are therefore biologically plausible mediators of the observed reduction in gastrointestinal and respiratory morbidity in the intervention group.

No significant inter-group improvements were detected for other micronutrients. Several explanations are plausible: (i) the contribution of these nutrients in the product was more modest relative to daily requirements (e.g., zinc 44% RDA, vitamin A 52% RDA, iron 61% RDA), (ii) their absorption and circulating levels may have been influenced by homeostatic regulation (particularly zinc), (iii) both study arms received dietary counselling, which may have improved intake of these nutrients in the control group as well, diluting the between-group differences, and (iv) inflammatory status and day-to-day variability may have affected serum biomarkers of these nutrients. Thus, while systemic improvements in B12, vitamin E, and selenium reflect a clear product effect, the absence of between-group differences for other nutrients highlights the combined influence of formulation strength, background diet, and biomarker sensitivity.

The absence of changes in CRP, AGP, and sTfR indicates that the intervention did not influence systemic inflammation, which is consistent with the trial population being largely healthy at baseline. Interestingly, no significant differences were detected in intestinal permeability (lactulose: mannitol ratio), urinary neopterin, or salivary IgA between groups. This suggests that the morbidity benefits were unlikely to be mediated via measurable changes in mucosal barrier function or mucosal immune biomarkers and are more plausibly attributable to improvements in systemic micronutrient status and its downstream effects on immune resilience.

Improvements in dietary intake and certain serum nutrient levels were observed across both groups. Since dietary counselling was provided to all participants, it is plausible that enhanced awareness and compliance with dietary advice contributed to these improvements, potentially attenuating the between-group differences attributable to the fortified malt-based food. But since dietary counselling was provided to both test and control groups, the observed between-group differences can be attributed to the fortified product rather than counselling per se.

The present trial has several notable strengths. First, compliance with the fortified malt-based food was very high (>90%), ensuring adequate exposure to the intervention. Second, morbidity outcomes were prospectively captured with frequent follow-up, and data re-analysis using non-parametric methods addressed the skewed distribution of illness outcomes, thereby enhancing statistical validity. Third, the inclusion of multiple outcome domains—including morbidity, absenteeism, and mechanistic biomarkers (salivary IgA, neopterin, lactulose: mannitol ratio) — provides triangulated evidence for the effect of the intervention on immune function. Importantly, the intervention spanned both monsoon and winter months, periods of high infection transmission, thereby strengthening external relevance.

At the same time, several limitations merit consideration. The trial was conducted in four schools in an urban setting, which may limit broader generalisability, particularly rural or non-school-attending populations may be limited, and effects might differ where baseline deficiencies or infection burdens are higher. Although illness outcomes were cross-checked with school records, some reliance on parental reporting raises potential for reporting bias. The observed reduction in absenteeism, while statistically significant, was modest at the individual level and should be interpreted in light of the high baseline attendance rates.

5. Conclusion

This study demonstrates that supplementation with fortified malt-based food (FMBF) over a 9-month period significantly reduced gastrointestinal and respiratory infection-related morbidity, reflected in fewer ill days, fewer participants experiencing illness episodes irrespective of severity, and lower school absenteeism among urban Indian school children. The intervention also improved blood levels of vitamin B12, vitamin E, and selenium. These findings suggest that such micronutrient fortified nutrition supplements may help manage infection related outcomes better.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

All authors except AK and JG are/were employed by the funder (Hindustan Unilever Limited, (formerly GSK Consumer Healthcare). AK was the principal investigator for this clinical study and part of the clinical study center. JG conducted statistical analysis for the study.

Statement of ethical approval

The study was performed in accordance with the protocol, Good Clinical Practice (GCP) guidelines, local regulations governing clinical conduct, and the ethical principles that have their origin in the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Committee of Jehangir Clinical Development Centre (JCDC) Pvt Ltd., Pune, India (ECR/352/Inst/ MW2013) and protocol version 5.0, dated 10th Oct. 2017. The study objectives were explained to all participants, who voluntarily gave written informed consent prior to enrolment. The study was registered with <https://clinicaltrials.gov/study/NCT02542865>.

Statement of informed consent

The informed consent form was reviewed and approved by the Institutional Ethics Committee of JCDC (Pune, India). All participants voluntarily gave written informed consent prior to enrolment.

Authors' Contributions

VR, PV, DC, and VG were mainly involved in the design of the study. AK was involved in investigation, methodology, and review of the manuscript. JB was involved in clinical operations of the study. AK held overarching responsibility for the study and ensured the study was conducted with both scientific rigor and ethical integrity. JG was responsible for statistical analyses of results. DK and HSG interpreted the study results and participated in data curation. DK and HSG led the manuscript drafting, including intellectual content, literature searches, data interpretation, and graph generation. The final version of the manuscript was carefully reviewed and approved by all authors. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Ethical restrictions imposed by the IEC prevent public sharing of the data for this study. The data used in this publication is owned by HUL (Foods). Data access requests will be evaluated by HUL (Foods) in consideration of IEC requirements. Interested researchers will need to sign a research collaboration agreement with HUL (Foods). Requests can be sent to D.K.

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Appendix

Supplementary Table 1. Nutrient Composition of Fortified Malt Based Food (test product)

Nutrients	FMBF (per 54g)	% RDA per daily serve *	Nutrients	FMBF (per 54g)	% RDA per daily serve *
Energy (Kcal)	203.6	8.9	Niacin (mg)	9.0	60.4
Fat (g)	1.1	2.9	Biotin (mcg)	5.0	15.7
Protein (g)	5.9	17.3	Pantothenic acid (mg)	1.0	16.4
Carbohydrate (g)	42.7	32.8	Phosphorus (mg)	151	15.1
Vitamin A (mcg)	400	51.8	Magnesium (mg)	35.0	13.1
Vitamin D (mcg)	5.0	33.5	Potassium (mg)	243.0	6.9
Vitamin E (mg)	1.4	18.0	Calcium (mg)	400.0	48.8
Vitamin C (mg)	80	137.8	Iron (mg)	14.0	60.5
Vitamin B6 (mg)	2.0	97.0	Iodine (mcg)	75.0	67.0
Vitamin B12 (mcg)	1.0	46.6	Sodium (mg)	216.0	10.8
Folic acid (mcg)	200	88.3	Selenium (mcg)	40	99.9
Vitamin B1 (mg)	1.0	46.2	Copper (mg)	0.5	20.6
Vitamin B2 (mg)	2	75.0	Zinc (mg)	4.0	44.1

*FMBF: Fortified-Malt based food, RDA: Recommended Dietary Allowance, *% RDA per daily serve calculated using average Recommended Dietary Allowances for Indian children (6-16 years) [ICMR-NIN Expert Group (2020) Nutrient Requirement for Indians, Recommended Dietary Allowances (RDA) and Estimated Average Requirements (EAR) 2020].*

Supplementary Table 2: Primary and secondary outcomes due to GI and ARI in test group (n=445) and control group (n=462) at months 3, 6, 9

	Interval	Group	Mean	Difference	P-value
Number of ill days due to GI	Month 3	Test	0.04 (0.0151)	-0.408 (0.0556)	<0.001
		Control	0.446 (0.0581)		
	Month 6	Test	0.184 (0.0404)	-0.803 (0.081)	<0.001
		Control	0.991 (0.0834)		
	Month 9	Test	0.249 (0.0549)	-0.83 (0.0865)	<0.001
		Control	1.078 (0.0857)		
Number of ill days due to respiratory illnesses	Month 3	Test	0.904 (0.146)	-2.54 (0.194)	<0.001
		Control	3.418 (0.2839)		
	Month 6	Test	1.807 (0.2054)	-5.22 (0.241)	<0.001
		Control	6.98 (0.3618)		
	Month 9	Test	2.054 (0.234)	-5.2 (0.242)	<0.001
		Control	7.21 (0.364)		
Frequency (per month) of GI illnesses	Month 3	Test	0.003 (0.0011)	-0.048 (0.0065)	<0.001
		Control	0.051 (0.0062)		
	Month 6	Test	0.012 (0.0021)	-0.087 (0.0077)	<0.001
		Control	0.099 (0.0073)		
	Month 9	Test	0.013 (0.0022)	-0.092 (0.0087)	<0.001
		Control	0.105 (0.0073)		
Frequency (per month) of respiratory illnesses	Month 3	Test	0.032 (0.0047)	-0.234 (0.0146)	<0.001
		Control	0.265 (0.0134)		
	Month 6	Test	0.055 (0.0051)	-0.279 (0.0133)	<0.001
		Control	0.331 (0.012)		
	Month 9	Test	0.059 (0.0051)	-0.277 (0.0132)	<0.001
		Control	0.334 (0.0119)		
School absenteeism (days) due to GI	Month 3	Test	0 (0)	-0.151 (0.0394)	<0.001
		Control	0.149 (0.0383)		
	Month 6	Test	0.04 (0.0161)	-0.153 (0.0373)	<0.001
		Control	0.186 (0.0394)		
	Month 9	Test	0.043 (0.0162)	-0.152 (0.0037)	<0.001
		Control	0.188 (0.0394)		
School absenteeism (days) due to respiratory illnesses	Month 3	Test	0.004 (0.0032)	-0.222 (0.0415)	<0.001
		Control	0.003 (0.0042)		
	Month 6	Test	0.09 (0.0194)	-0.329 (0.048)	<0.001
		Control	0.403 (0.0478)		
	Month 9	Test	0.09 (0.0194)	-0.33 (0.0479)	<0.001
		Control			

		Control	0.405 (0.0478)		
Number of ill days due to GI and ARI	Month 3	Test	0.94 (0.1509)	-2.95 (0.196)	<0.001
		Control	3.86 (0.3007)		
	Month 6	Test	1.99 (0.2133)	-6.01 (0.230)	<0.001
		Control	7.97 (0.3821)		
	Month 9	Test	2.28 (0.2475)	-6.01 (0.234)	<0.001
		Control	8.28 (0.3845)		
Frequency (per month) due to GI and ARI	Month 3	Test	0.037 (0.0051)	-0.32 (0.018)	<0.001
		Control	0.35 (0.0166)		
	Month 6	Test	0.067 (0.0058)	-0.37 (0.016)	<0.001
		Control	0.44 (0.0146)		
	Month 9	Test	0.07 (0.0058)	-0.37 (0.016)	<0.001
		Control	0.44 (0.0145)		
School absenteeism (days) due to GI and ARI	Month 3	Test	0.004 (0.0032)	-0.37 (0.055)	<0.001
		Control	0.37 (0.0578)		
	Month 6	Test	0.13 (0.0287)	-0.48 (0.0609)	<0.001
		Control	0.59 (0.0623)		
	Month 9	Test	0.13 (0.0287)	-0.48 (0.061)	<0.001
		Control	0.59 (0.0623)		
Values are adjusted means and standard error (SE); CI= Confidence Interval, Test group: FMBF + DC and Control group; DC alone. Analysis was performed using ANCOVA model with cluster (school) as a random effect and adjusted for baseline IDDS and gender using zero-inflated model. *values were significant at p<0.05 between the test and control groups					

Supplementary Table 3: Mean change in gut integrity parameters in test and control group from baseline due to GI and respiratory illnesses at month 9 (mITT population)

Immunity parameters	Test (n=445)		Control (n=462)		Mean difference (SE)	p-value
	Adjusted mean (SE)	p-value	Adjusted mean (SE)	p-value		
Lactulose: Mannitol test	0.006 (0.005)	0.4975	0.0048 (0.005)	0.6066	0.001 (0.007)	0.822
Urine neopterin test	0.135 (0.023)	0.0462	0.157 (0.023)	0.0372	-0.022 (0.033)	0.502
Salivary IgA	10.9 (1.02)	0.0087	10.1 (1.0)	0.0096	0.804 (1.43)	0.573
Values are adjusted means and standard error (SE); CI= Confidence Interval. Analysis was performed using ANCOVA model with cluster (school) as a random effect; product group and gender as fixed effects, and baseline IDDS as covariate, Test group: FMBF + DC and Control group; DC alone. *values were significant at $p<0.05$						