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REGULAR ARTICLE

Prenatal early food and multiple micronutrient supplementation trial reduced infant mortality in Bangladesh, but did not influence morbidity

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ABSTRACT

Aim: A previous maternal and infant nutrition intervention in rural Matlab, Bangladesh, showed that prenatal nutrient supplements improved child survival, but had no effect on size at birth. This secondary analysis examined whether prenatal multiple micronutrient supplements (MMS), on their own or combined with an early invitation to receive prenatal food supplements, affected child morbidity.

Methods: This randomised trial enrolled 4436 pregnant women from November 2001 to October 2003 and allocated them to early or standard invitations to food supplements, in the ninth and 20th weeks of pregnancy, respectively, and supplements of either the standard 60 mg iron with 400 μg folic acid, 30 mg iron with 400 μg folic acid or MMS. Quasi-Poisson regression was used to analyse morbidity.

Results: There were 3560 single live births and 3516 had morbidity data. The incidence rates of fever, diarrhoea and acute lower respiratory tract infection were 15.3, 3.6 and 2.3 episodes per person-year, respectively. The separate or combined interventions had no effect on morbidity up to 24 months.

Conclusion: Early invitations to prenatal food supplements or prenatal MMS had no effect on common infections in rural Bangladesh, suggesting that earlier findings on improved child survival were not mediated by an effect on child morbidity.

BACKGROUND

The nutritional status of women before and during pregnancy is critical for foetal and child growth and survival (1). Iron deficiency anaemia in pregnancy increases the risk of poor pregnancy outcomes (1), and the World Health Organization has recommended iron folic acid supplements for all pregnant women for several decades and continues to do so (2). Many pregnant women living in poor settings are also deficient in macronutrients and other micronutrients in addition to iron (1). Prenatal multiple micronutrient supplements (MMS) were developed for trial purposes for settings with co-existing micronutrient deficiencies (3). Compared to iron supplements, with or without folic acid, pooled analyses have shown that prenatal MMS have a small favourable effect on the risk of stillbirths, low birth weight and being small-for-gestational age, but have no effect on neonatal mortality (4). Possible health effects beyond the foetal period have not been studied so frequently. Food supplements during pregnancy have lowered the risk of stillbirths and increased foetal growth, especially among undernourished mothers (5). Data on the timing of prenatal food supplements are scarce, but evidence from famine studies and animal studies suggests that nutritional deficiencies at different time points in pregnancy have different effects on the offspring later on (6,7).

Abbreviations

ALRI, Acute lower respiratory tract infection; CI, Confidence interval; Fe30FA, Micronutrient supplement with 30 mg iron and 400 μg folic acid; Fe60FA, Micronutrient supplement with 60 mg iron and 400 μg folic acid; icddr,b, International Centre for Diarrhoeal Diseases Research, Bangladesh; MINIMat trial, Maternal and infant nutrition interventions in Matlab trial; MMS, Multiple micronutrient supplements; OR, Odds ratio; RR, Relative risk; SD, Standard deviation.

Key notes

- We have previously shown that an early invitation to receive earlier prenatal food supplements and prenatal multiple micronutrients improved child mortality.
- This secondary analysis focused on morbidity rates of 3516 children and showed that these interventions, separately or combined, were not associated with the incidence of common early childhood infections.
- The results suggest that the earlier effects on mortality were not mediated by an effect on child morbidity.

Bangladesh is a low-income country where co-existing nutrient deficiencies are common among pregnant women and children (8,9) with almost one-quarter of children being born with a low birth weight (10). The Maternal and Infant Nutrition Interventions in Matlab (MINIMat) trial was a randomised community-based trial in rural Bangladesh. It studied the effect of the timing of early versus standard invitation to receive prenatal food supplements and the type of micronutrient supplementation, namely iron folic acid versus MMS or a combination of these, on birth weight, infant survival and maternal haemoglobin status. Early invitations to receive food supplements or MMS had no differential effect on birth weight or maternal haemoglobin status. However, MMS combined with an early invitation to receive food supplements resulted in a considerable reduction in mortality in infants and children under five compared to standard iron folic acid supplements with the standard invitation to receive food supplements (11). The interventions also had effects on child growth, early prenatal food supplements lowered the occurrence of stunting, while MMS increased stunting in children up to five years of age (12).

Morbidity from common infections could act as a mediator that affects growth and mortality. Only a few trials have previously studied the effects of prenatal MMS on child morbidity. In trials in Nepal, prenatal MMS had no effect on child morbidity in the first weeks of life when compared to prenatal vitamin A supplements (13) or at a mean age of 2.5 years when compared to iron folic acid supplements (14). A trial among women with the human immunodeficiency virus infection in Tanzania found that prenatal multivitamin supplements lowered the risk of diarrhoea in children (15). No studies that we know of have analysed the effect of the timing of prenatal food supplements or the effect of the timing of prenatal food supplements combined with multiple micronutrients on child morbidity.

This study analyses the effects of prenatal food and micronutrient interventions on child morbidity, which was one of the secondary outcomes of the MINIMat trial. We hypothesised that early timing of prenatal food supplements and prenatal MMS, separately or in combination, would have a favourable effect on morbidity in children up to 24 months of age in rural Bangladesh, compared to the standard timing of food supplements and the standard iron folic acid supplements.

METHODS

Study setting and participants

The MINIMat trial was set in Matlab, a rural subdistrict in Bangladesh, where a well-established health and demographic surveillance system is run by the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr, b). If a woman reported having missed her menstrual period or suspected she was pregnant during a monthly surveillance system data collection, she was offered a pregnancy test and an ultrasound examination. When a pregnancy with a viable foetus of less than 14 weeks of gestation was confirmed, women without severe illness were invited to participate in the trial. Twins were excluded from follow-up studies after birth, as their expected differences to singletons, with regard to gestational age and size at birth, could influence their later development. For this analysis, all singleton children with data on morbidity were included.

Study design and interventions

The trial had a 2 × 3 factorial design with two food groups and three micronutrient groups, resulting in a total of six groups. At the time of the trial, the Government provided pregnant women with food supplements and the women typically chose to start taking these around 20 weeks of gestation. For the trial, the participants were randomised to receive either the standard invitation to food supplements or were invited to start them as soon as their pregnancy was confirmed around nine weeks of gestation. The supplement was available in community nutrition centres six days a week. It contained 608 calories and 18 g of protein from roasted rice powder (80 g), roasted pulse powder (40 g), molasses (20 g) and soya bean oil (12 mL). The women were also randomised to receive one of these three daily micronutrient supplements starting from 14 weeks of gestation: (i) 60 mg iron fumarate with 400 μg folic acid (Fe60FA, which was standard in this area for all pregnant women), (ii) 30 mg iron fumarate with 400 μg folic acid (Fe30FA) or (iii) MMS containing 30 mg iron fumarate, 400 μg folic acid, 800 μg RE vitamin A, 200 IU vitamin D, 10 mg vitamin E, 70 mg vitamin C, 1.4 mg vitamin B1, 1.4 mg vitamin B2, 18 mg niacin, 1.9 mg vitamin B6, 2.6 μg vitamin B12, 15 mg zinc, 2 mg copper, 65 μg selenium and 150 μg iodine (3). The women received a new bottle of micronutrient capsules monthly. More details of the trial have previously been published (11).

Data collection and outcomes

Trained field workers collected the data using structured questionnaires. Information on maternal age, parity, height, weight, education and household assets was obtained at enrolment, and household assets were analysed to create a score index (16).

The newborn infants were examined at home one week after the birth by a field worker who collected data on the following signs of illness: lethargy or unconsciousness, bulging fontanel, grunting, chest indrawing, fever or unusually cold skin, skin pustules, purulent eye discharge, red or purulent umbilicus and jaundice, defined as yellow colouring in the palms or soles. The respiratory rate was measured, and the child was considered to have rapid breathing if two consecutive measurements were at least 60 breaths per minute (17). The mother was also asked whether the newborn infant had experienced convulsions or difficulties breathing. Newborn morbidity was categorised as any signs of illness. Local infections were defined as having skin pustules, purulent eye discharge and/or red or purulent umbilicus, while severe illness was defined as convulsions, lethargy or unconsciousness, chest indrawing, bulging

fontanel, grunting and/or rapid breathing (18). If a child had more than one missing value on the signs of illness in any of the newborn morbidity categories, they were considered to have a missing value on that outcome category.

To assess the morbidity of the children up to 24 months of age, the field workers conducted monthly visits for the first year and quarterly visits in the second year, making 16 visits in total. During these visits, they asked the mother whether the child had had a fever, diarrhoea, cough or difficult breathing during the last seven days. If the mother reported a cough or difficult breathing, she was asked about the presence of rapid breathing or chest indrawing. Acute lower respiratory tract infection (ALRI) was defined as the presence of a cough and/or difficult breathing with rapid breathing and/or chest indrawing (17). Diarrhoea was defined as at least three loose stools in 24 hours and the mothers were asked about whether there was any blood in the stools during diarrhoea. The outcomes analysed for morbidity in children of 1–24 months of age were diarrhoea, diarrhoea with blood, fever and ALRI. The presence of morbidity during the seven-day recall period was considered as one episode regardless of its duration.

Sample size and randomisation

The sample size calculation for the trial was based on the primary aim of detecting a difference of 70 g in birth weight, which was considered as the minimum clinically important difference. A standard deviation (SD) of 400 g was assumed in the calculations. Further details have previously been reported (11). The amount of person-time in the current analyses allowed for the detection of a difference in the incidence of diarrhoea of 0.35 between the food groups, using the standard timing of supplements as the reference, and 0.41 between the micronutrient groups, using Fe60FA as reference. It also allowed for a 0.28 difference in the incidence of ALRI between the food groups and 0.33 between the micronutrient groups for children of 1–24 months of age.

An independent statistician used a computer-based register to randomly allocate participants to one of the six intervention groups in permuted blocks of 12 and the randomisation codes were kept safe in the icddr,b administrative office. The participants and data collectors were blinded for the micronutrient supplementation and the micronutrient capsules looked identical and came in identical bottles.

Statistical analysis

For the baseline characteristics, a mean with SD was calculated for continuous variables and proportions were calculated for categorical variables. To test for differences in the baseline characteristics between the mothers included in the analysis and the ones lost to follow-up, Pearson's chi-square test was performed for categorical variables and Welch's two-sample *t*-test was used for continuous variables.

The prevalence rates of the signs of newborn illness were calculated as percentages of the total sample and the intervention groups. Logistic regression was used to calculate the odds ratios (OR) of having any signs of illness, local infections and severe illness as binary yes/no outcomes, in the food groups with standard supplement timing as the reference and micronutrient groups with Fe60FA as the reference. An interaction between the main effects was tested by adding an interaction term to the regression model (food*micronutrient).

For the morbidity analysis of children of 1–24 months of age, the incidence rate of illness was calculated as the mean number of episodes of illness per person-year, with 95% confidence intervals (95% CI) in the total sample and the food and micronutrient groups. A quasi-Poisson regression was used to calculate and compare the relative risks (RR) of morbidity across the different intervention groups, with the incidence as the dependent variable and the food and micronutrient groups as the independent variables, again using the standard timing of supplements and Fe60FA as references, respectively. A quasi-Poisson regression was used instead of a Poisson regression to adjust for overdispersion (19). The interaction between the interventions was tested in the same way as described earlier. When an interaction was detected, the effect estimate (RR) of the combination showing a significant interaction was calculated and evaluated.

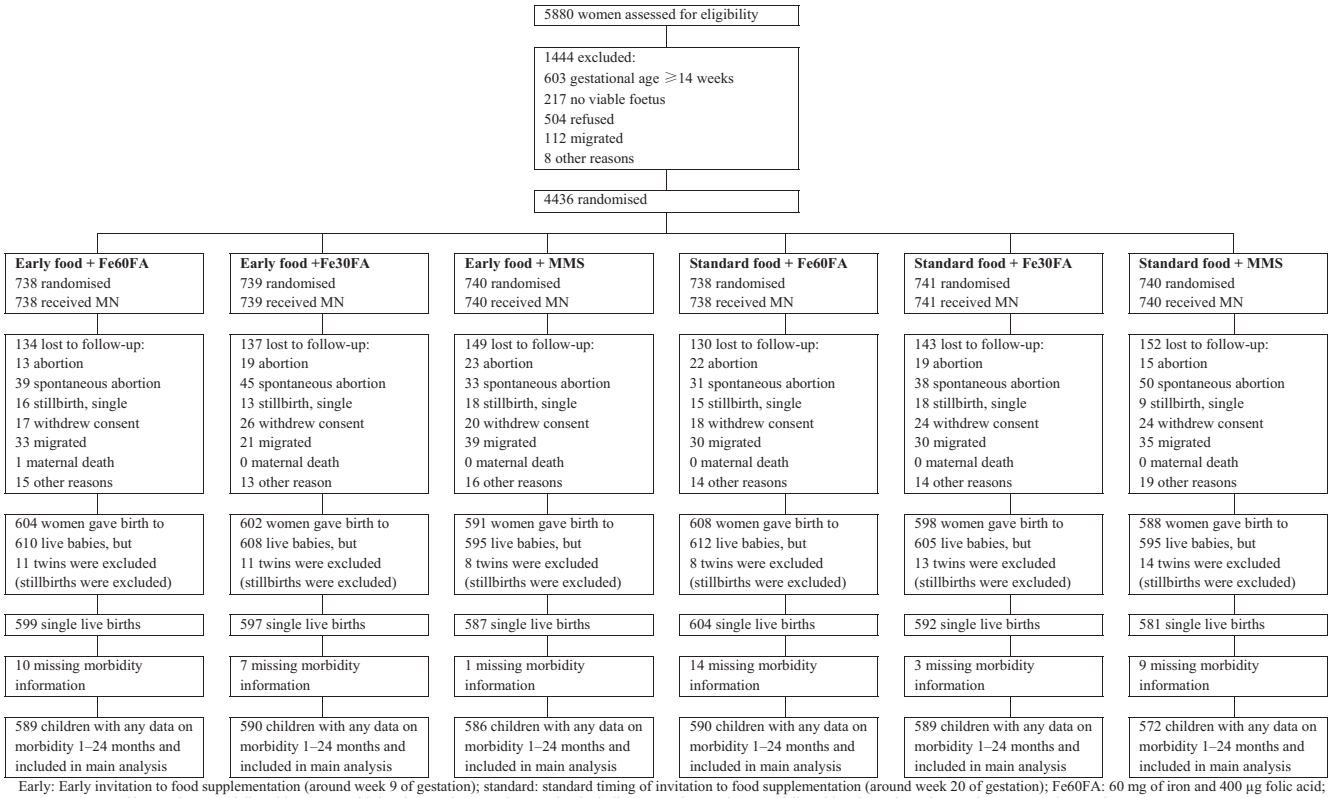
A two-sided p-value of <0.05 was considered statistically significant and 95% CI was used in all the analyses. Statistical analyses were conducted using R version 3.1.1 (R Core Team, Vienna, Austria) with package R Commander (20).

Ethical considerations

The Research and Ethics Review Committees of icddr,b approved the trial protocol, and the trial was registered in the International Standard Randomised Control Trial Number database (ISRCTN16581394). Informed consent was obtained from all women who participated at enrolment and they were told that they could withdraw from the trial, or any component of the trial, at any time without it affecting their free health care. Pregnant women with severe anaemia were excluded from the trial and referred for further care. Continuous monitoring for adverse effects was carried out and the field workers advised participants to seek health care if they developed a severe illness.

RESULTS

Between November 2001 and October 2003, a total of 4436 women were randomised to receive one of the six combinations of food and micronutrient supplements (Fig. 1), but 845 women were lost to follow-up, mainly due to pregnancy loss, moving out of the area or because they withdrew their consent. The remaining 3591 women gave birth to 3625 babies between April 2002 and June 2004. After birth, 65 twin children were excluded from the growth and morbidity data collection and 44 children were lost to follow-up,



Early: Early invitation to food supplementation (around week 9 of gestation); standard: standard timing of invitation to food supplementation (around week 20 of gestation); Fe60FA: 60 mg of iron and 400 μg folic acid; Fe30FA: 30 mg of iron and 400 μg folic acid; MMS: multiple micronutrient supplementation including 30 mg iron and 400 μg folic acid and 13 other micronutrients; MN: micronutrient

Figure 1 Study flow.

which meant that we had morbidity data on 3516 singleton children. Overall, the losses in the morbidity follow-up were small, but they were especially small in the group that was allocated to an early invitation to food supplements combined with multiple micronutrients, which had the lowest number of neonatal deaths (11). Data on signs of illness seven days after birth were available for 2186 newborn infants. The local tradition of visiting family around the time of the birth reduced the number of follow-ups. The baseline characteristics of those with data on neonatal illness did not differ from those without such data.

The baseline characteristics were similar across the six intervention groups (Table 1). The mean maternal height was 149.8 cm (SD 5.3), the mean weight was 45.3 kg (SD 6.8) and 28.0% of mothers were underweight, with a body mass index of less than 18.5 at enrolment. The mothers had an average of 5.2 years (SD 4.1) of education. The median number of follow-up visits was 16 in all of the intervention groups, ranging from one to 16 visits with 90% having at least 11 visits. This resulted in a total of 966 (90%) of 1079 possible person-years of observation.

Overall, one-fifth of all newborns had any signs of illness at the follow-up visits seven days after birth (Table S1). The most common signs of illness were jaundice (9.5% prevalence), red or purulent umbilicus (4.5%) and skin pustules (4.4%). No association was found between the timing of food supplements or type of micronutrient supplements, or a combination of these, and signs of illness in the newborn infant.

The most commonly reported symptom of an illness among children of 1–24 months of age was fever, with an average of 15.3 episodes per person-year. The timing of food supplements and type of micronutrient supplements, separately or in combination, did not have an effect on fever (Table 2). The incidence of diarrhoea was 3.6 episodes per person-year. Early food supplementation (versus standard) or MMS (versus Fe60FA), or a combination of these, were not found to have an effect on diarrhoea morbidity. However, Fe30FA (versus Fe60FA) was found to increase the risk of diarrhoea (3.91 versus 3.40 episodes per person-year, RR 1.66, 95% CI 1.16–2.38). A significant statistical interaction between the early food group and Fe30FA was detected, and early food plus Fe30FA (versus standard food plus Fe60FA) showed a significantly increased risk of diarrhoea (RR 1.87, 95% CI 1.11–3.16). The incidence of episodes of the more severe form of diarrhoea with blood in the stools was 0.24 per person-year. We found no differences between the food or micronutrient groups. A significant statistical interaction between the early food group and Fe30FA and between the early food group and MMS

Table 1 Baseline characteristics of households and mothers by the randomisation groups in the MINIMat trial in rural Bangladesh

Characteristics	Levels	Total	Intervention groups					
			Early invitation to food supplementation			Standard timing of food supplementation		
			Fe60FA	Fe30FA	MMS	Fe60FA	Fe30FA	MMS
Maternal age in years, mean (SD)		25.8 (5.9)	25.9 (6.0)	25.7 (5.8)	26.3 (6.1)	25.7 (5.9)	25.9 (5.9)	25.5 (5.7)
Maternal BMI, mean (SD)		20.2 (2.6)	20.2 (2.6)	20.0 (2.5)	20.2 (2.7)	20.2 (2.7)	20.0 (2.7)	20.3 (2.5)
Mothers <145 cm, n/n (%)		506/3221 (15.7)	84/536 (15.7)	92/531 (17.3)	77/543 (14.2)	86/554 (15.5)	81/531 (15.3)	86/526 (16.3)
Parity, n/n (%)	0	1025/3225 (31.8)	179/536 (33.4)	172/533 (32.3)	159/542 (29.3)	171/557 (30.7)	167/531 (31.5)	177/526 (33.7)
	1–2	1598/3225 (49.6)	255/536 (47.6)	260/533 (48.8)	262/542 (48.3)	293/557 (52.6)	264/531 (49.7)	264/526 (50.2)
	≥3	602/3225 (18.7)	102/536 (19.0)	101/533 (18.9)	121/542 (22.3)	93/557 (16.7)	100/531 (18.8)	85/526 (16.2)
Household asset score quintiles, n/n (%)	Lowest	648/3226 (20.1)	102/536 (19.0)	116/533 (21.8)	124/543 (22.8)	110/557 (19.7)	107/531 (20.2)	89/526 (16.9)
	Lower-middle	660/3226 (20.5)	108/536 (20.1)	110/533 (20.6)	103/543 (19.0)	115/557 (20.6)	107/531 (20.2)	117/526 (22.2)
	Middle	642/3226 (19.9)	110/536 (20.5)	115/533 (21.6)	102/543 (18.8)	105/557 (18.9)	105/531 (19.8)	105/526 (20.0)
	Higher-middle	644/3226 (20.0)	115/536 (21.5)	102/533 (19.1)	104/543 (19.2)	110/557 (19.7)	105/531 (19.8)	108/526 (20.5)
	Highest	632/3226 (19.6)	101/536 (18.8)	90/533 (16.9)	110/543 (20.3)	117/557 (21.0)	107/531 (20.2)	107/526 (20.3)
Maternal education, n/n (%)	0 years	1003/3418 (29.3)	156/568 (27.5)	174/574 (30.3)	181/570 (31.8)	171/573 (29.8)	165/577 (28.6)	156/577 (28.1)
	1–5 years	779/3418 (22.8)	126/568 (22.2)	141/574 (24.6)	123/570 (21.6)	131/573 (22.9)	143/577 (24.8)	115/577 (20.7)
	≥6 years	1636/3418 (47.9)	286/568 (50.4)	259/574 (45.1)	266/570 (46.7)	271/573 (47.3)	269/577 (46.6)	285/577 (51.3)

BMI = Body mass index, weight in kg/(height in m)^2; Fe60FA = 60 mg of iron and 400 μg folic acid; Fe30FA = 30 mg of iron and 400 μg folic acid; MMS = Multiple micronutrient supplementation including 30 mg iron and 400 μg folic acid and 13 other micronutrients.

was detected for diarrhoea with blood. Early food plus Fe30FA (versus standard food plus Fe60FA) showed a decreased risk of diarrhoea with blood (RR 0.88, 95% CI 0.77–0.99). The effect estimate of early food plus MMS (versus standard food plus Fe60FA) was, however, not statistically significant (RR 0.91, 95% CI 0.80–1.04). The incidence of ALRI was 2.3 episodes per person-year. The interventions, separately or combined, were not found to have an effect on the incidence of ALRI.

DISCUSSION

We have shown that in a population in Bangladesh where malnourishment was common, an early invitation to receive prenatal food supplements or MMS, or a combination of these, had no association with newborn morbidity and did not reduce the incidence of fever, diarrhoea or ALRI in children of 1–24 months of age. This was despite a previously reported reduction in neonatal and infant mortality in children born to mothers allocated to an early invitation to food supplements combined with MMS (11).

The results were based on a community-based trial, conducted in an area with a well-established health and demographic surveillance system that enabled early identification of pregnancy. Community members were accustomed to, and compliant with, study activities linked to service provision, which strengthened the quality of the data. The randomised design minimised the risk of potential confounding and double masking of the micronutrient intervention reduced the risk of reporting or observation bias. All analyses were carried out according to the original randomisation regardless of adherence, thus reflecting the true, unbiased effect of the intervention. We had a relatively large sample size and regular data collection, 99% of the singleton children were included in the morbidity follow-up, and we achieved 90% of the possible person-years of follow-up. The data on morbidity being reported by the infants' carers was a limitation and this could have over- or underestimated the incidence rates. A recall period of seven days, which has been found to be the optimal recall time with this kind of reported data, was used to minimise recall bias (21).

We have previously shown that an early invitation to receive prenatal food supplements combined with prenatal MMS, compared to the standard invitation to receive food supplements and standard iron folic acid supplements, lowered the infant mortality rate (16.8 per 1000 live births versus 44.1 per 1000 live births, hazard ratio 0.38, 95% CI 0.18–0.78) (11). The early invitation to receive food supplements with MMS seemed to have influenced foetal and infant health without having differential effects on size at birth. In a substudy, the thymic volume was assessed by ultrasound at eight, 24 and 52 weeks of age, showing that the prenatal supplements did not affect thymic size (22). Thymic size in early infancy was associated with subsequent survival (23). The associations between supplements and child growth were more complex. The early invitation to receive food supplements in pregnancy reduced the

Table 2 Incidence of reported morbidity among children aged 1–24 months in the supplement groups in the MINIMat trial in rural Bangladesh

Morbidity, interventions	n	Person-years	Incidence* (95% CI)	RR† (95% CI)	p Value‡
Diarrhoea					
Total	3516	965.81	3.64 (3.49–3.78)		
Food					
Standard	1751	477.94	3.58 (3.38–3.79)	1.00	
Early	1765	487.87	3.69 (3.47–3.92)	1.12 (0.84–1.51)	
Micronutrient					
Fe60FA	1179	325.57	3.40 (3.15–3.64)	1.00	
Fe30FA	1179	322.58	3.91 (3.65–4.17)	1.66 (1.16–2.38)	
MMS	1158	317.67	3.60 (3.36–3.87)	1.22 (0.86–1.74)	
Early × Fe30FA					0.041
Early × MMS					0.317
Diarrhoea with blood					
Total	3516	965.81	0.24 (0.20–0.27)		
Food					
Standard	1751	477.94	0.27 (0.23–0.32)	1.00	
Early	1765	487.87	0.20 (0.16–0.25)	0.93 (0.87–1.00)	
Micronutrient					
Fe60FA	1179	325.57	0.24 (0.19–0.30)	1.00	
Fe30FA	1179	322.58	0.23 (0.18–0.30)	0.99 (0.92–1.08)	
MMS	1158	317.67	0.24 (0.18–0.30)	0.99 (0.92–1.08)	
Early × Fe30FA					0.029
Early × MMS					0.002
Fever					
Total	3516	965.81	15.31 (14.98–15.61)		
Food					
Standard	1751	477.94	15.14 (14.69–15.57)	1.00	
Early	1765	487.87	15.47 (15.01–15.92)	1.40 (0.75–2.60)	
Micronutrient					
Fe60FA	1179	325.57	15.21 (14.66–15.75)	1.00	
Fe30FA	1179	322.58	15.59 (15.03–16.14)	1.46 (0.68–3.14)	
MMS	1158	317.67	15.12 (14.61–15.63)	0.92 (0.43–1.96)	
Early × Fe30FA					0.314
Early × MMS					0.365
Acute lower respiratory tract infection					
Total	3516	965.81	2.33 (2.20–2.48)		
Food					
Standard	1751	477.94	2.33 (2.13–2.55)	1.00	
Early	1765	487.87	2.34 (2.14–2.54)	1.01 (0.76–1.34)	
Micronutrient					
Fe60FA	1179	325.57	2.25 (2.02–2.51)	1.00	
Fe30FA	1179	322.58	2.56 (2.30–2.83)	1.37 (0.97–1.95)	
MMS	1158	317.67	2.18 (1.92–2.43)	0.93 (0.67–1.31)	
Early × Fe30FA					0.640
Early × MMS					0.481

Fe60FA = 60 mg of iron and 400 μg folic acid; Fe30FA = 30 mg of iron and 400 μg folic acid; MMS = Multiple micronutrient supplementation including 30 mg iron and 400 μg folic acid and 13 other micronutrients.

*Episodes per person-year.

†Relative risk estimated with quasi-Poisson regression, food or micronutrient intervention as predictor, morbidity as outcome.

‡Interaction between main effects, standard and Fe60FA as references.

occurrence of stunting in children 0–54 months of age, while prenatal MMS increased stunting. These effects were judged to be of public health importance and could indicate programming in early foetal life (12). Our hypothesis in this paper relates to these previous findings, which showed that MINIMat prenatal interventions had effects on child growth and mortality (11,12). An effect on morbidity, if present, could potentially mediate part of the effects on mortality and growth. However, such a mediating role did not seem to be present.

In a prenatal supplement trial in Nepal with different micronutrient alternatives, MMS with a slightly different composition were found to have no effect on infectious disease symptoms in the first 10 days of life or in seven or

30 days preceding a follow-up at six weeks of life (13). The prevalence of different signs of illness, assessed mainly through maternal recall, was higher in the Nepali study than in ours, suggesting that our estimates of newborn infectious disease morbidity were low.

The micronutrient supplement alternative with 30 mg iron with 400 μg folic acid (Fe30FA) was included in this trial mainly in relation to the maternal haemoglobin outcome in the third trimester. In the present analysis, we noted a slightly higher incidence of diarrhoea in the Fe30FA group than in the group receiving Fe60FA. The absolute difference was 0.56 episodes per person-year, implying somewhat limited public health importance should this finding be true. The mechanism by which Fe30FA would increase the risk of diarrhoea is unclear. We have previously reported that no differences were found between the Fe60FA and Fe30FA groups at six months of age with regard to anaemia or deficiencies in iron, zinc, vitamin B12 or folate (24).

The incidence of diarrhoea in our study was 3.6 episodes per person-year, which was similar to the level of 4.25 episodes per person-year reported by another study conducted in rural Bangladesh (25). We did not find that MMS had any effect on diarrhoea morbidity. A trial in Tanzania found a 14% lowered risk of diarrhoea among children aged six weeks to two years born to mothers infected with the human immunodeficiency virus who had received micronutrient supplements with nine different vitamins during pregnancy (15). Some studies have reported that prenatal zinc had a protective effect against diarrhoea in infants (26,27) and low birth weight infants (28). The MMS in our study contained 15 mg of zinc, which was slightly lower than the dose used in some other studies (26,28).

The incidence of ALRI in our study was higher than in a previous study from the same area (29), where field worker assessments of signs of respiratory illness were used. This may explain the higher incidence and possible over-reporting in our study. We did not find any effect on ALRI, similar to other studies that have investigated the effect of prenatal micronutrient supplements on respiratory tract infections (13,15,27,28).

The relationship between morbidity and mortality is complex. A reduction in mortality does not always mean a reduction in morbidity, and this was demonstrated in some earlier vitamin A supplement trials (30). An intervention may not reduce the incidence of diseases, but it can perhaps diminish severity and, therefore, reduce the amount of related deaths.

CONCLUSION

In this trial in rural Bangladesh, we found that an early invitation to receive prenatal food supplements or prenatal MMS, or a combination of these, did not reduce the incidence of fever, diarrhoea or ALRI in infancy and early childhood. This indicates that the previously reported effects of nutritional interventions during early pregnancy on mortality and linear growth were not mediated by reduced morbidity in infancy and early childhood.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Prevalence of signs of illness in newborns seven days of age and association with food and micronutrient supplementations in the MINIMat trial in rural Bangladesh.