ORIGINAL RESEARCH ARTICLE

Effects of maternal micronutrient supplementation on fetal loss and under-2-years child mortality: Long-term follow-up of a randomised controlled trial from Guinea-Bissau

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ABSTRACT

A number of trials on maternal multi-micronutrient supplementation (MMS) have found a benefical effect on birth weight, but few have demonstrated a beneficial effect on infant survival. We examined the effect of two different preparations of antenatal MMS on fetal loss and under-2-years child mortality, as compared with iron-folic acid supplementation among 2,100 pregnant women in Guinea-Bissau. Women receiving a 1xRDA MMS preparation (consisting of 14 vitamins and minerals) had a marginally reduced risk of fetal loss (Relative risk (RR) 0.65, 95% CI 0.40; 1.05), and women receiving a 2xRDA MMS preparation had a similar effect (RR 0.67, 95% CI 0.42; 1.08), the pooled effect being 0.66 (95% CI 0.44; 0.99). None of the supplements reduced under-2-years mortality or the combination of fetal loss and under-2-years mortality. There was a marginally negative effect of both the 1xRDA (RR 2.10, 95% CI 0.99; 4.46) and the 2xRDA (RR 2.02, 95% CI 0.95; 4.32) MMS preparation on mortality specifically between 92-365 days of age. (*Afr. J. Reprod. Health* 2010; 14[2]:17-26).

RÉSUMÉ

Effets de la recherche micro-nourricière matérielle sur la perte du fœtus et la mortalité infantile de moins de deux ans : suite d'observation d'un essai contrôlé au hasard de la Guinée Bissau. Un certain nombre d'essais sur la recharge multi micro – nourricière maternelle (MMN) ont porté des bénéfices à l'égard de la perte de poids, mais très peu ont fait preuve d'un effet salutaire sur la survie de l'enfant. Nous avons examiné l'effet de deux différentes préparations de la MMN prénatale sur la perte du fœtus et la mortalité infantile de moins de deux ans comparé à la recharge en acide folique de fer chez 2,100 femmes enceintes en Guinée Bissau. Les femmes qui prenaient la préparation 1xRDA MMS (qui se compose de 14 vitamines et des substances minérales) risquaient une perte réduite du fœtus de manière négligeable (Risque relatif (RR) 0,65, 95% CI 0,40 ; 1,05), et les femmes qui prenaient la préparation 2xRDA MMS ont eu l'effet pareil (RR 0,67, 95% C10, 42 ; 1,08), l'effet réuni étant 0,66 (95% CI 0,44 ; 0,99). Aucun des suppléments n'a réduit la mortalité de moins de deux ans ou la combinaison de la perte du fœtus et la mortalité de moins de deux ans. Il y avait un effet négatif négligeable de 1xRDA (RR 2,10, 95% CI 0,99.4,46) et 2xRDA (RR 2, 02, 95% CI 0,95 ; 4,32) sur la mortalité en particulier entre l'âge de 92 – 365 jours. (*Afr. J. Reprod. Health* 2010; 14[2]:17-26).

KEYWORDS: Micronutrients, Pregnancy, Infant Mortality, Fetal Death, Randomized Controlled Trial, Survival Analysis.

INTRODUCTION

UNICEF has suggested that the current iron-folic acid prenatal supplement (IFS) should be replaced by a prenatal multi-micronutrient supplement (MMS), and developed the UNIMMAP supplement to be tested in efficacy and effectiveness trials[1;2]. However, a shift in policy from IFS to MMS is stalled by the inconclusive evidence on the effects of MMS. While a number of MMS trials, have found an increase in mean birth weight and a decrease in the proportion of low birth weight as compared to IFS[3-8], not all have demonstrated a beneficial effect on infant survival[5-9]. A potentially harmful effect of MMS on perinatal mortality has even been debated[10-13].

The ambiguous findings on vital outcomes call for a broadened evaluation of prenatal supplements, based not only on birthweight and mortality in the first three months of life but also on fetal loss and overall mortality during childhood. For example, an increased peri- and neonatal mortality observed in data from Nepal has been speculated to be caused by increased intrauterine survival followed by increased risk of death[11]. Also, programming effects of fetal malnutrition on later morbidity and mortality[14;15], suggests that effects of fetal undernutrition are not limited to the peri- and neonatal stages. Finally, misclassification between miscarriage and stillbirths are common and the definitions used to distinguish miscarriage and stillbirth may not reflect biological effects of micronutrient supplementation.

From a randomised controlled double masked trial in Guinea-Bissau, we have previously reported the effects of MMS on pregnancy outcome including birth weight, neonatal and perinatal mortality[6]. However, in that publication the potential effects of fetal loss – i.e., either miscarriage or stillbirth – is not considered and neither is mortality during childhood. To address this further, we made a two-year follow up of that trial, and examined the effect of UNIMMAP and double dose UNIMMAP supplementation on fetal loss and under-2-years mortality.

METHODS

Study setting and population

The trial population was recruited from January 2001 to February 2002 within four suburban districts followed by the Bandim Health Project (BHP) in collaboration with the Danish Epidemiology Science Centre, Statens Serum Institut, Copenhagen, Denmark[16]. In a subsample of the study population, it was found that 14% of the women had low vitamin A status, 25% had depleted iron stores, 77% had tissue iron deficiency, and 70% had marginal or low folate status, indicating that the population most likely was affected by inadequate micronutrient status[17].

The BHP surveillance system continuously registers pregnancies, births and child-deaths. New pregnancies are mapped monthly through home visits carried out by field assistants, and child health and survival are monitored through home visits every third month from birth to three years of age.

All pregnant women in the study districts were invited to participate in the trial when they attended antenatal care at the two health centres in the districts. Women who were identified as pregnant during the ongoing pregnancy surveillance were also invited to participate. Out of a total of 2,402 registered pregnancies in the period of recruitment, 2,169 (90%) pregnant women were identified by the trial team.

Ethics

The trial was approved by the Ministry of Health in Guinea-Bissau, and by the Danish Central Medical Ethics Committee. Informed consent was given orally and written information was attached to the antenatal cards of participating women. Women with severe anemia (hemoglobin <70 g/l) received 60mg iron per day in addition to their intervention. Participants received an impregnated bed net at inclusion and were provided weekly anti-malarial prophylaxis with chloroquine phosphate (300mg base) throughout pregnancy, in accordance with the national policy for pregnant women in Guinea-Bissau. Women with more than 10 parasites per 200 leucocytes at inclusion were offered anti-malarial treatment with chloroquine.

Data collection

Each pregnant woman was interviewed and/or examined by the trial team at inclusion, post partum and eight weeks post partum. At inclusion one of four midwifes from the BHP collected data on various background factors, anthropometry, hemoglobin, malaria parasitaemia and day of last menstruation.

Table 1. Composition and daily doses of maternal micronutrient supplements.

Nutrient	Iron-folate	UNIMMAP-1	UNIMMAP-2
Vitamin A (µg RE)	0	800	1600
Vitamin D (IU)	0	200	400
Vitamin E (mg)	0	10	20
Vitamin B1 (mg)	0	1.4	2.8
Vitamin B2 (mg)	0	1.4	2.8
Niacin (mg)	0	18	36
Folic acid (µg)	400	400	800
Vitamin B6 (mg)	0	1.9	3.8
Vitamin B12 (µg)	0	2.6	5.2
Vitamin C (mg)	0	70	140
Zinc (mg)	0	15	30
Iron (mg)	60	30	30
Copper (mg)	0	2.0	4.0
Selenium (µg)	0	65	130
Iodine (µg)	0	150	300

Post partum, and eight weeks post partum, another four nurses or midwives collected data including pregnancy outcome (i.a. miscarriages, stillbirths, live-births, deaths). Subsequent deaths were detected at the routine home visits by the BHP surveillance system, undertaken every third month for the first year of age and thereafter every six months.

Intervention and Randomisation

Participating women were individually randomised to receive a daily supplement of one of the following three identical looking micronutrient tablets from the first antenatal visit and throughout pregnancy; *iron-folate* (60 mg iron and 400 µg folic acid), *UNIMMAP-1 (*one recommended dietary allowances (RDA) of nine vitamins and five minerals) as proposed by UNICEF for future programs[2], or *UNIMMAP-2* (two RDAs of the UNIMMAP) (Table 1). Iron was kept at one RDA in both UNIMMAP groups to avoid potentially detrimental effect of iron[18-20]. All supplements were manufactured by Danish Pharmaceutical Industries Ltd. (Copenhagen, Denmark). Supplements were provided in colour-coded containers unknown to investigators, field staff and participants. Participants were block randomised in blocks of 150 subjects in each. Participants were instructed to pick a coloured piece of paper from an envelope containing 50 pieces of papers of each of the three colours indicating the intervention code[17]. Supplements were distributed with a fixed amount of excess tablets at biweekly visits, and remaining supplements were counted and replenished.

Endpoints

Information on fetal loss was drawn from hospital records if occuring at a hospital. Date of fetal loss occurring at home was reported by the women. Fetal loss was defined as miscarriages (≤28 weeks of gestation) and stillbirths (>28 weeks of gestation). Date of under-2-years death was drawn from the BHP death registration, consisting of a brief verbal autopsy interview implemented by two trained field assistants two weeks to three months after death[16]. Thus, registration of neonatal mortality from the intervention trial was used only to verify dates for neonatal deaths. Under-2-years mortality was defined as all deaths among live born from birth through 730 days.

To analyse mortality within specific age-periods in childhood, age-bands were constructed as follows: Neonatal mortality was defined as deaths in the first 28 days of life among live borns, and early infant mortality was defined as all deaths before 92 days among infants surviving the first 28 days of life. Late infant mortality was defined as all deaths before 366 days among infants surviving the first 91 days of life, and early child mortality was defined as all deaths before reaching 731 days among infants surviving the first 365 days of life. Birthweight and perinatal mortality which were the initial primary outcomes in the trial have been reported elsewhere[6].

Statistical analysis

Characteristics of the pregnant women were compared across intervention groups. Differences were

detected by comparison of percentages and absolute figures. Crude incidence rates were calculated as the number of deaths per 1,000 fetuses or children. Cox-regression with robust estimation of standard errors to account for correlation between twins was used to estimate the hazard ratio and 95% confidence intervals of loosing a fetus for women receiving UNIMMAP-1 and UNIMMAP-2 as compared with women receiving iron-folate supplements. Time since enrolment defined the underlying time, and fetal death indicated a failure event. To account for a higher probability of being included in the study population among fetuses that survived longer, delayed entry was allowed for, so that fetuses were only at risk from their gestational age at enrolment and until fetal death or birth. Thus each fetus only contributes to risk-time from date of enrolment.

A similar approach was used to estimate hazard ratios and 95% confidence intervals of death from birth through the age of two years. However, in the analysis of child mortality, time since birth, ie. age, was used as the underlying time. To compare the Cox-regression analyses of fetal loss and under-2-year mortality, generalized estimating equations (GEE) allowing for correlation between twins was applied. GEE methods was also used to analyse the effect of UNIMMAP supplementation on fetal loss or under-2-year mortaliy, thus estimating the overall effect on pre- and postnatal mortality.

To analyse age specific effects of the UNIMMAP-1 and UNIMMAP-2 on mortality, follow-up time was stratified in age-bands of 0-28 days, 29-91 days, 92-365 days and 366-730 days. Cox-regression models were thereafter fitted for each age-band as described above, and interaction between intervention and age-bands was tested using the likelihood-ratio test.

Sample size calculations for this trial have previously been reported[6]. During the two years follow-up, children were supplemented with vitamin A as part of yearly routine campaigns in the study area. To outrule a potential interacting effect of vitamin A and MMS supplementation, we made additional analyses censoring follow-up time for children when they received vitamin A supplementation in campaigns[21].

A p-value <0.05 was considered significant in regression analyses. Hazard ratios and odds ratios were reported as relative risks, as they both approximate relative risks for rare events[22]. Proportional hazard assumptions were inspected in graphical plots. All analyses were done in Stata 10.0 (Stata Corp. LP).

RESULTS

The trial profile is shown in Figure 1. Of the 2,169 pregnancies identified by the intervention trial team, 69 were >37 weeks pregnant when identified and were excluded from the study sample. Thus, a total of 2,100 pregnant women consented and were randomised to one of the three supplements. The trial profile diverged slightly from a previous publication on the same trial[6], since some mothers that were not found at that time had been identified later.

A total of 386 mother-fetus pairs migrated or were not localizable and were therefore excluded from the study, and 57 mother-fetus pairs were not included in the analyses due to missing follow-up data. Of the remaining 1,657 (78.9%) pregnant women in the study, 1,560 gave birth to a total of 1,586 live infants. Of these, 58 were from twin pregnancies.

Randomisation resulted in relatively similar baseline characteristics in the three intervention groups (Table 2), although the proportion of pregnant women <20 years was slightly higher in the iron-folate supplementation group as compared to the other two intervention groups. Also, a lower proportion of the women in the UNIMMAP-1 group were less than ≤16 weeks pregnant at time of inclusion in the study, and a lower proportion in the iron-folate group had experienced prior child loss. Compliance with supplementation was high (median 76%) (Table 2).

Fetuses were followed from the day of entry into the study and until fetal death or birth. The total follow-up time was 539.1 fetus-years. In total, 94 singleton pregnancies ended in a fetal loss, while three women with twin pregnancies lost five fetuses, adding up to a total of 99 fetal losses. Of these, 26 (26.3%) were miscarriages and 73 (73.7%) were stillbirths. Hazards were considered proportional throughout pregnancy. Live born children were followed until the age of two, or until censored due to loss to follow-up. The total follow-up time was 2,535 child-years distributed as 116.0, 252.6, 1,009.5 and 1,156.9 child-years within the age-bands 0-28 days, 29-91 days, 92-365 days and

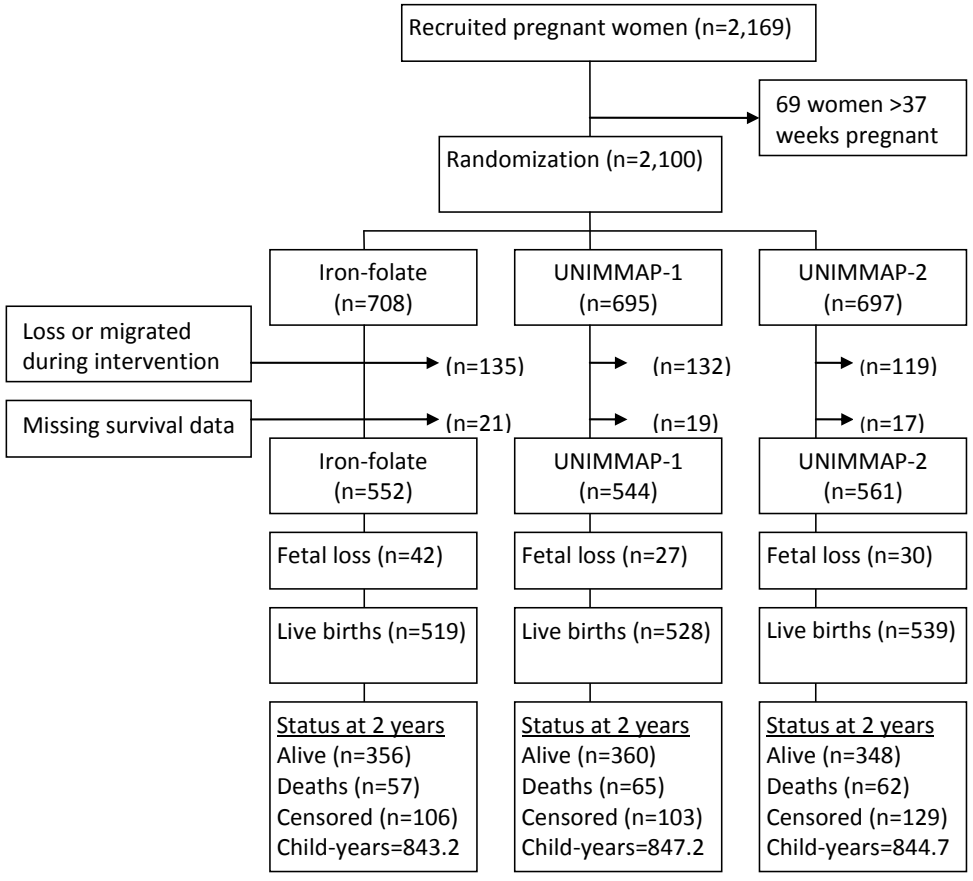

Figure 1. Trial Profile.

366-730 days respectively. A total of 184 children died before reaching their second birthday, yielding an under-2-year mortality rate of 116.0 per 1,000 live births.

Fetal loss

Pregnant women receiving UNIMMAP-1 had a marginally significant (p=0.077) lower risk of fetal loss (RR 0.65, 95% CI 0.40; 1.05), and women receiving UNIMMAP-2 supplements showed a similar lower risk (RR 0.67, 95% CI 0.42; 1.08), as compared to the iron-folate group. When data from the UNIMMAP treatment groups was pooled, women receiving either UNIMMAP-1 or UNIMMAP-2 had a significantly lower risk of fetal loss (RR 0.66, 95% CI 0.44; 0.99) as compared to the iron-folate group (Table 3).

Under-2-years mortality

Cox regression analysis of under-2-years mortality yielded no significant difference in the risk of under-2-years mortality among children of women receiving UNIMMAP-1 (RR 1.16, 95% CI 0.81; 1.67), UNIMMAP-2 (RR 1.12, 95% CI 0.78; 1.60) or UNIMMAP-1 + UNIMMAP-2 (RR 1.14, 95% CI 0.83; 1.56) as compared with iron-folate supplementation (Table 3).

In the analysis of the overall mortality (fetal loss and under-2-years), we found no differences for children or fetuses of women

Table 2. Baseline characteristics of mothers according to intervention group.

	Iron-folate (n=708) *	UNIMMAP-1 (n=695) *	UNIMMAP-2 (n=697) *
Age in years (%, [n])			
<20	24.3 (172)	20.7 (145)	21.1 (147)
20-24	34.5 (244)	35.1 (244)	36.7 (256)
25-29	24.2 (171)	26.8 (186)	24.5 (171)
≥30	17.0 (120)	17.0 (118)	17.2 (120)
Years of school (%, [n])			
0	30.4 (153)	31.6 (164)	30.6 (152)
1-4	22.9 (115)	19.3 (95)	21.1 (105)
5-7	28.2 (142)	29.2 (144)	27.8 (138)
>7	18.5 (93)	19.9 (98)	20.5 (102)
Parity (%, [n])			
0	32.2 (182)	31.3 (178)	28.8 (173)
1-2	37.6 (213)	36.8 (209)	38.7 (219)
3-4	18.6 (105)	19.7 (112)	20.9 (118)
>4	11.7 (66)	12.2 (69)	11.7 (66)
Prior loss of child (%, [n])	21.6 (109)	27.8 (138)	26.8 (133)
Gestational age ≤16 weeks (%, [n])	21.04 (145)	17.6 (119)	20.7 (138)
Rainy season of conception (%, [n])	51.7 (357)	47.7 (324)	47.1 (316)
Man living in household (%, [n])	58.2 (271)	60.3 (275)	58.4 (263)
Weight (cm) †	59.6±9.3	60.0±9.9	60.2±9.6
Height (cm) †	160.3±5.7	160.4±5.9	160.5± 6.0
Hip circumference (cm) †	96.8± 8.4	96.5± 8.0	97.5± 8.0
Hemoglobin (g/l) †	105.8±16.5	106.9±16.1	105.9±15.9
Compliance (%)†	78.6±27.5	75.6±30.0	74.0±26.7

*Frequencies in parentheses
†Mean±SD

receiving UNIMMAP-1 (RR 0.92, 95% CI 0.67; 1.26), UNIMMAP-2 (RR 0.90, 95% CI 0.66; 1.23) or UNIMMAP-1 + UNIMMAP-2 (RR 0.91, 95% CI 0.69; 1.19) as compared with iron-folate supplementation (Table 3).

Analyses of fetal loss and under-2-years mortality using generalized estimating equations yielded similar results and censoring of children at the time of vitamin A supplementation did not alter the results either (data not shown).

To analyse whether child age modified the effect of the interventions on child mortality, the effect of the intervention on child mortality was stratified on the age-bands 0-28 days, 29-91 days, 92-365 days and 366-730 days, allowing estimation of the effect of intervention on child mortality stratified on neonatal mortality, early infant mortality, late infant mortality and early child mortality. Although only marginally significant (p = 0.053) there was a higher risk of late infant mortality for infants of mothers receiving the UNIMMAP-1 supplement (RR 2.10, CI 0.99; 4.46) or the UNIMMAP-2 supplement (RR 2.02, CI 0.95; 4.32) as compared to infants of mothers receiving the iron-folate intervention. When the UNIMMAP treatment groups were pooled, the effect was significant in the late infant mortality age band (RR 2.06, CI 1.03;

Table 3. Relative risk of prenatal and under-2-years death for fetuses/children of mothers from the UNIMMAP-1 and UNIMMAP-2 intervention groups as compared to fetuses/children of mothers from the iron-folate group.

	N	Deaths (Rate*)		RR (95% CI)
Fetal death†				
Iron-folate	561	42	(74.9)	1
UNIMMAP-1	555	27	(48.6)	0.65 (0.40; 1.05)
UNIMMAP-2	569	30	(52.7)	0.67 (0.42; 1.08)
UNIMMAP-1+2	1124	57	(50.7)	0.66 (0.44; 0.99)
Under 2 years mortality†				
Iron-folate	519	57	(109.8)	1
UNIMMAP-1	528	65	(123.1)	1.16 (0.81; 1.67)
UNIMMAP-2	539	62	(115.0)	1.12 (0.78; 1.60)
UNIMMAP-1+2	1067	127	(119.0)	1.14 (0.83; 1.56)
Fetal death + Under 2 years mortality‡				
Iron-folate	561	99	(176.5)	1
UNIMMAP-1	555	92	(165.8)	0.92 (0.67; 1.26)
UNIMMAP-2	569	92	(161.7)	0.90 (0.66; 1.23)
UNIMMAP-1+2	1124	184	(163.7)	0.91 (0.69; 1.19)

*Deaths per 1,000 fetuses or births
†Based on cox-regression models
‡Based on GEE models

4.12). However, the test for intervention-age-band interaction was not significant (p=0.11). There were no significant differences in the effects for children of mothers receiving UNIMMAP-1 or UNIMMAP-2 as compared with iron-folate on the risk of neonatal mortality, early infant mortality or early child mortality (Table 4).

DISCUSSION

This study suggests that pregnant women receiving one or two doses of the UNIMMAP intervention have a reduced risk of fetal loss as compared with pregnant women receiving IFS. We found neither beneficial nor detrimental effect of either of the UNIMMAP supplements on under-2-year child mortality nor overall mortality (fetal loss and under-2-years mortality). However, there was a trend towards a higher risk of death in late infancy among children of mothers who received UNIMMAP-1 or UNIMMAP-2.

Few studies have addressed the effect of maternal multi-micronutrient supplementation on fetal loss in low income countries. In a review, the authors do not find evidence of an effect of vitamin supplementation on fetal loss, but the reviewed studies are from widely dissimilar populations and the majority of the included studies examined single vitamin supplementation only[23]. Another review found no effect of supplements containing three or more micronutrients on perinatal mortality[24]. A beneficial effect on fetal loss has previously been reported in Tanzania among HIV-positive women receiving an alternative MMS composition with high doses of vitamin B, C and E[7]. When this supplement was tested on HIV-negative women, there was no significant effect on fetal loss or peri- and neonatal mortality, albeit a similar trend was seen[25]. In Gambia, women receiving energy/protein supplementation had a reduced risk of stillbirths[26], and in Indonesia there was a positive effects of UNIMMAP on

Table 4. Relative risk and 95% confidence intervals of dying within selected age-groups for children of mothers from the UNIMMAP-1 and UNIMMAP-2 intervention groups as compared to children of mothers from the iron-folate group.

	N	Deaths (Rate*)		RR (95% CI)
Neonatal mortality (0-28 days)				
Iron-folate	519	25	(48.2)	1
UNIMMAP-1	528	29	(54.9)	1.18 (0.68; 2.05)
UNIMMAP-2	539	23	(42.7)	0.92 (0.52; 1.63)
UNIMMAP-1+2	1067	52	(48.7)	1.05 (0.64; 1.70)
Early infant mortality (29-91 days)				
Iron-folate	492	9	(18.3)	1
UNIMMAP-1	492	6	(12.2)	0.68 (0.24; 1.91)
UNIMMAP-2	512	9	(17.6)	1.00 (0.40; 2.50)
UNIMMAP-1+2	1004	15	(14.9)	0.84 (0.37; 1.91)
Late infant mortality (92-365 days)				
Iron-folate	474	10	(21.1)	1
UNIMMAP-1	473	21	(44.4)	2.10 (0.99; 4.46)
UNIMMAP-2	482	20	(41.5)	2.02 (0.95; 4.32)
UNIMMAP-1+2	955	41	(42.9)	2.06 (1.03; 4.12)
Early child mortality (366-730 days)				
Iron-folate	421	13	(30.9)	1
UNIMMAP-1	421	9	(21.3)	0.68 (0.29; 1.59)
UNIMMAP-2	414	10	(24.1)	0.78 (0.34; 1.77)
UNIMMAP-1+2	835	19	(22.7)	0.73 (0.36; 1.48)

*Deaths per 1,000 alive.

fetal loss and neonatal mortality combined[8].

Given the relatively late identification of pregnancies, the proportion of fetal death in the iron-folic acid group in our trial was high (7.5%). This could indicate that the observed effect on fetal death was in fact due to increased risk of fetal death in the iron-folic acid group due to the higher amounts of iron received in this group. This is however not consistent with marginally significant benefical effect on fetal loss of multimicronutrients reported in Indonesia, where both the iron-folic acid group and the multimicronutrient group received 30 mg of iron[8].

We found no effect of UNIMMAP supplementation on under-2-years mortality, even though there was a 53 g (UNIMMAP 1) and 95 g (UNIMMAP 2) effect of supplementation on birth weight in this population[6]. The Nepalese trials found that MMS was associated with increased neonatal mortality. We found no evidence for that; if anything, MMS was associated with decreased mortality in the first 3 months of life and after 12 months of life. This effect was balanced by a trend towards a negative effect in late infancy. If indeed the interventions increase late infant mortality, then a number of explanations could apply. Detrimental interactions between one or more of the nutrients in the supplement and exposure to specific infections may have occurred, and thus increased the risk of death. Antagonistic interactions between micronutrients and infections have

been reported previously[27]. Also, it is possible that we observe a beneficial effect of iron-folate rather than a detrimental effect of the UNIMMAP intervention, provided that a beneficial effect of 60 rather than 30 mg of iron may act specifically in late infancy. Finally, two trials on vitamin A supplementation at birth in Guinea Bissau[28] and Zimbabwe[29] found similar patterns of slightly beneficial effect in the first months of life and then a shift to a slightly negative effect up to the age of one, patterns which resemble the mortality pattern presented in Table 4.

Women that were lost to follow-up differed from women followed-up in weight, height, age and parity, but loss to follow up was evenly distributed across intervention groups (data not shown). Therefore, it is unlikely that loss to follow-up have skewed the results. Still, young age, low maternal weight and height may constitute proxy variables for micronutrient deficiency, and a higher proportion of women lost to follow-up may thus suffer from deficiencies. If the presented effects of the UNIMMAP supplements pertain specifically to women with micronutrient deficiency, the effects of the UNIMMAP supplements may have been underestimated.

It is likely that the effect of UNIMMAP-1 and -2 on birth weight reflects a partial reduction of fetal-growth-limiting maternal micronutrient deficiencies. In the present study it seems that maternal micronutrient supplementation can bring about beneficial but possibly also detrimental effects on survival during fetal stages and early childhood. Further research is needed to identify the most appropriate composition, doses and timing of such supplement, in terms of not only increasing birth weight, but also improving maternal and infant health and survival.

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