

Effects of fortified milk on morbidity in young children in north India: community based, randomised, double masked placebo controlled trial

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ABSTRACT

Objective To evaluate the efficacy of milk fortified with specific multiple micronutrients on morbidity in children compared with the same milk without fortification.

Design Community based, double masked, individually randomised trial.

Setting Peri-urban settlement in north India.

Participants Children (n=633) aged 1-3 randomly allocated to receive fortified milk (n=316) or control milk (n=317).

Intervention One year of fortified milk providing additional 7.8 mg zinc, 9.6 mg iron, 4.2 µg selenium, 0.27 mg copper, 156 µg vitamin A, 40.2 mg vitamin C, 7.5 mg vitamin E per day (three feeds).

Main outcome measures Days with severe illnesses, incidence and prevalence of diarrhoea, and acute lower respiratory illness.

Results Study groups were comparable at baseline; compliance in the groups was similar. Mean number of episodes of diarrhoea per child was 4.46 (SD 3.8) in the intervention (fortified milk) group and 5.36 (SD 4.1) in the control group. Mean number of episodes of acute lower respiratory illness was 0.62 (SD 1.1) and 0.83 (SD 1.4), respectively. The fortified milk reduced the odds for days with severe illnesses by 15% (95% confidence interval 5% to 24%), the incidence of diarrhoea by 18% (7% to 27%), and the incidence of acute lower respiratory illness by 26% (3% to 43%). Consistently greater beneficial effects were observed in children aged ≤24 months than in older children.

Conclusion Milk is well accepted as a means of delivery of micronutrients. Consumption of milk fortified with specific micronutrients can significantly reduce the burden of common morbidities among preschool children, especially in the first two years of life.

Trial registration NCT00255385.

INTRODUCTION

Reducing the higher risk of infectious disease by alleviating deficiencies in micronutrients among young children in developing countries has assumed greater importance in research and implementation in public health. Because of the inherent technical and practical limitations of a supplementation strategy,¹⁻³ the limited success of nutritional education programmes,⁴ and the difficulty in promoting animal based foods,⁵ delivery of zinc and iron through fortification of commonly consumed foods is the only practical and sustainable option.

To evaluate acceptability and efficacy of delivering specific micronutrients, including zinc and iron, through

fortified milk we conducted a community based, double masked, randomised controlled trial comparing fortified milk with the same milk without fortification for prevention of common childhood morbidities.

METHODS

Participants—The trial was carried out in a peri-urban population in New Delhi, India, from April 2002 to April 2004. Details of the population have been previously published.^{6,7} From a regularly updated demographic database we invited all permanently resident families with children aged 1-3 years to participate in the study. Irrespective of group allocation all children who had severe anaemia at baseline were given a therapeutic dose of iron for three months in addition to their milk supplement.

Baseline assessment, blood samples, and laboratory procedures—A detailed baseline assessment included examination and collection of socioeconomic and demographic information. Two independent observers measured weight to the nearest 10 g with an electronic scale and length or height to the nearest 0.1 cm with length boards. Researchers collected a venous blood sample at baseline and at the end of the study. See bmj.com for laboratory analysis.

Randomisation and masking—This study was implemented concurrently with another two-armed clinical trial to evaluate the efficacy of a different milk preparation fortified with probiotic (compared with preparation without fortification) in a non-factorial design with joint randomisation. Each treatment group (across the two trials) was identified by a letter code A, B, C, or D. We generated two separate randomisation lists—one for children with baseline Hb >70 g/l and another for children with baseline Hb ≤70 g/l. The supplementation sachets were identical in colour, size (weight 32 g), and taste and were labelled with a letter code. The randomisation code was not known to investigators or anyone in the field until the study was finished and the data analysed. We report here on children allocated to two of the four letter codes. From our sample size calculation we needed 325 children in each group (see bmj.com).

Intervention—We used 32 g single serving sachets of fortified milk powder. At enrolment, mothers were shown how to reconstitute the powdered milk. See bmj.com for composition of milk. Assistants delivered 21 sachets each week to each home and advised that the child should consume up to three

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sachets a day. Supplementation was continued for one year. We recorded the use of additional sachets given at the parents' request to children going away from home. The intervention (fortified milk in three servings a day) was designed to deliver zinc 9.6 mg (7.8 mg more than control group) and iron 9.6 mg. The fortified milk also included extra vitamin C to improve iron absorption, copper to counteract possible effects of zinc and iron on copper absorption, selenium, vitamin A, and vitamin E to help antioxidant and immune effects of zinc (see bmj.com for full details on composition).

Household surveillance during follow-up—During weekly visits to households, assistants distributed the milk sachets and collected unconsumed sachets and information on compliance. Other assistants visited homes twice a week to collect morbidity information. Both teams gathered information on compliance. There were two levels of supervision and random checking. About 10% of the houses were randomly visited to verify the overall information gathered. At each visit, supervisors recorded information for each of the previous three to four days since the last visit, including number of diarrhoeal stools, consistency of stools, blood in stools, pneumonia, fever, vomiting, and history of feeding. Mothers were advised to contact study physicians if they thought the child was

seriously ill between visits. Visits either to the study physicians or to private physicians were recorded. Treatment of diarrhoea, dysentery, and pneumonia was provided free to participating children.

Primary outcomes and definition of clinical outcomes—Primary outcomes were episodes of diarrhoea and acute lower respiratory tract infections or pneumonia and days with severe illness. Diarrhoea was defined as three or more loose or watery stools in 24 hours, and children were considered to have recovered after three days without diarrhoea. Acute lower respiratory tract infection was diagnosed if the child had reported difficulty in breathing and rapid breathing (≥ 40 /min). Severe illness consisted of temperature $\geq 38.4^\circ\text{C}$ or admission to hospital or respiratory rate ≥ 50 /min or chest indrawing. Dysentery was defined as diarrhoea with visible blood in stools, severe acute lower respiratory tract infections (worsening of existing infection or new onset of cough or difficulty in breathing with high respiration rate (≥ 50 /min) or chest indrawing), fever (axillary temperature $\geq 37.2^\circ\text{C}$), and high fever (axillary temperature $\geq 38.4^\circ\text{C}$).

Data management and statistical methods—For primary analysis we used alphabetical codes for groups still blinded to real group identity. We performed intent to treat analysis and included all data gathered during the intervention period of one year. For children leaving the area or withdrawing from the study, we included data until the date of censorship. Person-time analysis was performed with actual follow-up as denominator. For the effect on incidence of diarrhoea, acute lower respiratory tract infection, and measles, we estimated relative risk using Poisson regression; and for prevalence, we estimated odds ratio.

RESULTS

Out of 660 eligible children contacted, we received consent for 633 children (316 in intervention, 317 in control) to participate in the study and collected data on 190 324 child days of follow-up (see bmj.com). The children in both the groups were comparable at baseline for sociodemographic variables, haematology, and plasma zinc status. The mean number of sachets consumed was 2.58 in the intervention group and 2.54 in the control group. On 77.4% and 77.3% child days, respectively, an intake of three sachets was recorded. Only 9.5% of children in the intervention group and 6.0% in the control group did not have any episodes of diarrhoea. The mean number of episodes of diarrhoea and of acute lower respiratory tract infection was lower in the intervention than control group (table). Overall days with severe illness and the risk of measles were also lower. Adherence to the milk feeds was similar in the groups; 85.6% in the intervention group and 86.7% in the control group consumed two or three servings on more than 80% of days.

DISCUSSION

Children who received fortified milk compared with those who received same quantity and quality milk

Effect on morbidity according to allocation to fortified (intervention) or non-fortified (control) milk (robust estimates)

	Intervention (n=316)	Control (n=317)	Relative risk or odds ratio (95% CI)	P value
Gastrointestinal morbidity				
Episodes of diarrhoea:				
All children (aged 1-3 years)	1408	1700	0.82 (0.73 to 0.93)	0.002
Age ≤ 24 months	529	555	0.84 (0.71 to 0.96)	0.03
Age > 24 months	879	1145	0.80 (0.69 to 0.93)	0.004
Days of diarrhoea	3277	4010	0.81* (0.77 to 0.85)	0.00
Episodes of dysentery	121	133	0.91 (0.67 to 1.22)	0.52
Respiratory morbidity				
Episodes of acute lower respiratory illness:				
All children (aged 1-3 years)	195	262	0.74 (0.57 to 0.97)	0.03
Age ≤ 24 months	71	117	0.53 (0.35 to 0.81)	0.003
Age > 24 months	124	145	0.89 (0.67 to 1.19)	0.42
Days with respiration rate > 40 /min	279	368	0.75* (0.65 to 0.88)	0.00
Severe episodes of acute lower respiratory illness	79	110	0.72 (0.49 to 1.05)	0.09
Febrile illness and others				
Days with severe illness:				
All children (aged 1-3 years)	530	621	0.85* (0.76 to 0.95)	0.006
Age ≤ 24 months	186	254	0.64* (0.53 to 0.77)	0.00
Age > 24 months	344	367	0.97* (0.84 to 1.13)	0.73
Days with high fever	2899	3099	0.93* (0.88 to 0.98)	0.005
Measles	1	8	0.12 (0.02 to 0.99)	0.05
Antibiotics consumed (doses)	7166	7437	0.96* (0.92 to 0.99)	0.01

*Odds ratios.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Deficiency in specific micronutrients, especially iron and zinc, is prevalent in preschool children in developing countries and predisposes these children to common childhood infections

Supplementation with zinc leads to significant reduction in morbidity from diarrhoea or pneumonia

Supplementation is difficult to implement and has not been successful in prevention of iron deficiency

WHAT THIS STUDY ADDS

Fortified milk is well accepted as an intervention to deliver specific micronutrients with sustained compliance

Consumption of milk fortified with zinc, iron, and specific micronutrients is associated with decreased incidence of diarrhoea, acute lower respiratory tract infections, and days with severe illness

without specific fortification had 18% lower incidence of diarrhoea, 26% lower incidence of pneumonia, 7% fewer days with high fever, and 15% fewer days sick with severe illnesses.

The significantly lower rates of measles and use of antibiotics suggest that fortification resulted in a substantial prevention of morbidity and an overall improved immunity against common infections. The fact that all children in the study received about 1.89 MJ energy, 20 g protein, 49 g carbohydrates, and 19 g fat, in addition to their complementary foods or breast milk, suggests that these effects could be expected even in moderately well fed children.

Our study was in keeping with the recently ratified World Health Organization global strategy on infant and young child feeding, which notes that industrially processed complementary foods are an option for mothers who can afford them and have the knowledge and facilities to safely prepare and feed them.⁸ We used fortified milk to deliver zinc and iron with the addition of copper, vitamin A, selenium, vitamin E and vitamin C, though this limits our ability to determine the contributions of individual micronutrients.

There is a growing consensus that both zinc and iron should be given to vulnerable groups, including preschool children and that iron and zinc requirements may be difficult to meet from non-fortified complementary foods.⁹ Our results are consistent with results of trials of the effect of routine zinc supplementation on incidence of diarrhoea¹⁰⁻¹⁴ and acute lower respiratory tract infections.¹⁵ Given the design of this study we cannot estimate interaction between these minerals, but our results do suggest an overall benefit and thus a lack of any significant negative interaction between zinc and iron when in fortified milk.

Lack of selected micronutrients—especially zinc, selenium, iron, and the antioxidant vitamins—can lead to clinically important immune deficiency and infections in children. These nutrients act as antioxidants and cofactors at the level of cytokine regulation and can affect cytokine response and immune cell trafficking.¹⁶

Conclusion

The latest estimates of the percentage of gross domestic product lost to all forms of vitamin and mineral deficiency is 1-2% in the developing world.¹⁷ We have shown that micronutrients, especially zinc and iron, at levels that have been traditionally delivered by supplementation can be delivered successfully through fortified milk.

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Competing interests: None declared.

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- Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, et al. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. Zinc investigators' collaborative group. *J Pediatr* 1999;135:689-97.
- Allen LH. Iron supplements: scientific issues concerning efficacy and implications for research and programs. *J Nutr* 2002;132(suppl 4):813-9.
- World Health Organization. *Iron deficiency anaemia: assessment, prevention, and control*. Geneva, Switzerland: World Health Organization, 2001 (WHO/NID/01.3).
- Bhandari N, Mazumder S, Bahl R, Martinez J, Black RE, Bhan MK. An educational intervention to promote appropriate complementary feeding practices and physical growth in infants and young children in rural Haryana, India. *J Nutr* 2004;134:2342-8.
- Rivera JA, Hotz C, Gonzalez-Cossio T, Neufeld L, Garcia-Guerra A. The effect of micronutrient deficiencies on child growth: a review of results from community-based supplementation trials. *J Nutr* 2003;133(suppl 2):4010-20.
- Sazawal S, Black RE, Menon VP, Dhingra P, Caulfield LE, Dhingra U, et al. Zinc supplementation in infants born small for gestational age reduces mortality: a prospective, randomized, controlled trial. *Pediatrics* 2001;108:1280-6.
- Black MM, Sazawal S, Black RE, Khosla S, Kumar J, Menon V. Cognitive and motor development among small-for-gestational-age infants: impact of zinc supplementation, birth weight, and caregiving practices. *Pediatrics* 2004;113:1297-305.
- World Health Organization. *Global strategy for infant and young child feeding*. Geneva: World Health Organization, 2003 (WS 120).
- World Health Organization. *Complementary feeding of young children in developing countries: a review of current scientific knowledge*. Geneva: WHO, 1998 (WHO/NUT/98.1).
- Solomons NW, Jacob RA, Pineda O, Viteri FE. Studies on the bioavailability of zinc in man. Effects of the Guatemalan rural diet and of the iron-fortifying agent, NaFeEDTA. *J Nutr* 1979;109:1519-28.
- Davidsson L, Kastenmayer P, Hurrell RF. Sodium iron EDTA [NaFe(III)EDTA] as a food fortificant: the effect on the absorption and retention of zinc and calcium in women. *Am J Clin Nutr* 1994;60:231-7.
- Sazawal S, Black RE, Bhan MK, Jalla S, Sinha A, Bhandari N. Efficacy of zinc supplementation in reducing the incidence and prevalence of acute diarrhoea—a community-based, double-blind, controlled trial. *Am J Clin Nutr* 1997;66:413-8.
- Rosado JL, Lopez P, Munoz E, Martinez H, Allen LH. Zinc supplementation reduced morbidity, but neither zinc nor iron supplementation affected growth or body composition of Mexican preschoolers. *Am J Clin Nutr* 1997;65:13-9.
- Penny ME, Marin RM, Duran A, Peerson JM, Lanata CF, Lonnerdal B, et al. Randomized controlled trial of the effect of daily supplementation with zinc or multiple micronutrients on the morbidity, growth, and micronutrient status of young Peruvian children. *Am J Clin Nutr* 2004;79:457-65.
- Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A, Bhan MK. Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double-blind, controlled trial. *Pediatrics* 1998;102:1-5.
- Cunningham-Rundles S, McNeely DF, Moon A. Mechanisms of nutrient modulation of the immune response. *J Allergy Clin Immunol* 2005;115:1119-28.
- Adamson P. *Vitamins and mineral deficiency: a global progress report*. Ottawa, Canada/New York: UNICEF, 2004.

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