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Effectiveness and Efficacy of Zinc for the Treatment of Acute Diarrhea in Young Children

Tor Arne Strand, MD*‡; Ram Krisna Chandyo, MD*‡; Rajiv Bahl, MD, PhD§; Pushpa Raj Sharma, MBBS, DCH, FCPS‡; Ramesh Kant Adhikari, MD‡; Nita Bhandari, PhD§; Rune Johan Ulvik, MD, PhD¶; Kåre Mølbak, MD, PhD||; Maharaj Krishan Bhan, MD§; and Halvor Sommerfelt, MD, PhD*||

ABSTRACT. Intervention trials have shown that zinc is efficacious in treating acute diarrhea in children of developing countries. In a randomized, placebo-controlled trial, we assessed the effectiveness and efficacy of giving 3 Recommended Daily Allowances of elemental zinc to 6- to 35-month-old children with acute diarrhea.

Methods. Seventeen hundred ninety-two cases of acute diarrhea in Nepalese children were randomized to 4 study groups. Three groups were blinded and the children supplemented daily by field workers with placebo syrup, zinc syrup, or zinc syrup and a massive dose of vitamin A at enrollment. The fourth group was open and the caretaker gave the children zinc syrup daily. Day-wise information on morbidity was obtained by household visits every fifth day.

Results. The relative hazards for termination of diarrhea were 26% (95% confidence interval [CI]: 8%, 46%), 21% (95% CI: 4%, 38%), and 19% (95% CI: 2%, 40%) higher in the zinc, zinc-vitamin A, and zinc-caretaker groups, respectively, than in the placebo group. The relative risks of prolonged diarrhea (duration >7 days) in these groups were 0.57 (95% CI: 0.38, 0.86), 0.53 (95% CI: 0.35, 0.81), and 0.55 (0.37, 0.84); zinc accordingly reduced the risk of prolonged diarrhea with 43% to 47%. Five percent and 5.1% of all syrup administrations were followed by regurgitation in the zinc and zinc-vitamin A group, respectively, whereas this occurred after only 1.3% of placebo administrations. Vomiting during diarrhea was also more common in children receiving zinc.

Conclusions. Three Recommended Daily Allowances of zinc given daily by caretakers or by field workers substantially reduced the duration of diarrhea. The effect of zinc was not dependent on or enhanced by concomitant vitamin A administration. *Pediatrics* 2002;109:898–903; zinc, vitamin A, acute diarrhea, young children, randomized placebo controlled trial, effectiveness, Nepal, treatment.

ABBREVIATIONS. RDA, Recommended Daily Allowance.

From the *Center for International Health, University of Bergen, Bergen, Norway; ‡Department of Child Health, Tribhuvan University, Kathmandu, Nepal; §Department Paediatrics, All India Institute of Medical Sciences, New Delhi, India; ||Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark; and ¶Institute of Clinical Biochemistry, University of Bergen, Norway.

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Address correspondence to Halvor Sommerfelt, MD, PhD, Center for International Health, University of Bergen, Armauer Hansen Building, N-5021 Bergen, Norway. E-mail: halvor.sommerfelt@cih.uib.no
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Intervention trials indicate that zinc given during acute diarrhea is efficacious in reducing the duration and severity of the illness.^{1–7} Thus, therapeutic use of zinc has the potential of reducing the annual 2.5 million childhood diarrheal deaths.⁸ A recent pooled analysis showed a small beneficial effect of zinc given by health personnel on the risk of continuation of diarrhea. The overall reduction in the risk of prolonged diarrhea, defined as an episode lasting >7 days, was <20% and had a wide confidence interval that included 1.⁶ The effectiveness of zinc when given by caretakers has yet to be determined.

Zinc is involved in the release of vitamin A from the liver cells,⁹ in the synthesis of retinol-binding protein,¹⁰ and the effect of zinc in infectious diseases may be dependent on adequate vitamin A status.^{10,11} In some of the trials that showed a beneficial impact of zinc during diarrhea, the participants in the placebo as well as in the zinc group were given vitamin A or a micronutrient mixture that included vitamin A.^{1–3,6,7} It is possible that, in some of these trials, the replenishment of vitamin A stores were a prerequisite for the effects of zinc. A recent study from Bangladesh indicated that zinc and vitamin A supplementation interacted in reducing the prevalence of persistent diarrhea and dysentery in children.¹² However, other studies from Bangladesh failed to demonstrate an interaction between these 2 micronutrients given during diarrhea.^{5,13}

The effectiveness of zinc administration should be appropriately investigated before it is recommended routinely as an adjunct therapy for acute childhood diarrhea in developing countries. Moreover, an in-depth evaluation of possible adverse effects of zinc administration is needed and has been lacking in reports from previous trials.

In a placebo-controlled trial, we administered 3 Recommended Daily Allowances (RDAs)¹⁴ of elemental zinc, which is in the upper range of the doses given in previous trials. We chose a relatively large dose because zinc is lost in the stool during diarrhea,¹⁵ and because of the variable effect of zinc in previous studies.^{1–7} The supplement was given daily by field workers or by caretakers to assess efficacy and effectiveness, respectively, of zinc on the duration of acute childhood diarrhea, on the proportion of episodes that became prolonged, and on stool

frequency. We also monitored the children for adverse effects. Furthermore, we included a study group to ensure that the effect of zinc was not restricted to children that were simultaneously supplemented with vitamin A.

METHODS

This was a double-blind, randomized, placebo-controlled trial in children designed to measure the impact of daily zinc administration with or without a massive vitamin A dose at enrollment on the duration and severity of acute diarrhea. The effectiveness of the caretaker giving zinc to the child was assessed in an open group whereas the 3 other study groups (placebo, zinc, and vitamin A-zinc) were double-blinded (Fig 1).

The trial had ethical clearance from the Nepalese and Norwegian national health authorities. The implementation of all aspects of the project was in agreement with the International Ethical Guidelines for Research Involving Human Subjects as stated in the latest version of the Helsinki Declaration. Informed and, when possible, written consent was obtained from at least 1 of the parents.

Sample Size Calculations

The sample sizes were calculated for 80% power and 95% confidence. In the calculations we assumed that 20% of the cases in the placebo group had a duration of >7 days¹ and set the desired percentage of such prolonged episodes in each of the intervention groups to 12.5 (ie, 37.5% reduction), which resulted in a required group size of 405. With an expected 10% loss to follow-up, we decided to enroll 450 episodes in each of the 4 study groups. The power to detect any superadditive effect of zinc and vitamin A over zinc alone was lower; this comparison was not an objective of the trial.

Inclusion and Exclusion Criteria, Definitions, and Randomization

We enrolled children from the whole municipality of Bhaktapur, which is the third largest town in the Kathmandu valley in Nepal. Children were recruited by weekly household-based surveillance and at spontaneous visits to the study field clinic. Diarrhea was defined as the passage of 3 or more loose or watery stools in the 24-hour period before enrollment. Eligible children were screened in the clinic by a physician and included if the responsible caretaker was willing to let him/her participate. We included children between 6 and 35 months that had had diarrhea for <96 hours. Children were allocated to either of the 4 intervention groups (Fig 1) by simple randomization with blocks of 16.

A child was not included if he or she had received a massive dose of vitamin A during the previous 4 weeks, had severe illness requiring hospitalization, or if the family intended to leave Bhaktapur within 2 months. We allowed a child to be rerandomized and enrolled in the study only if >4 months had lapsed from recovery from the previous enrollment episode.

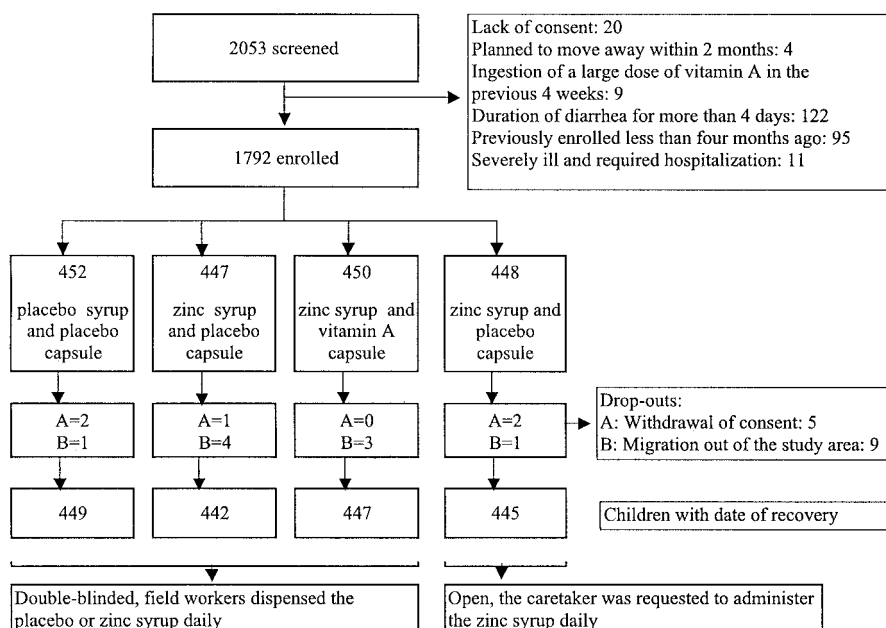
Recovery from diarrhea was defined as the first of the first 2 consecutive diarrhea-free days. A diarrhea-free day was a day when the child passed <3 loose and no watery stools.

Interventions, Blinding, and Cointerventions

Vitamin A or placebo administered from identical capsules were given on the enrollment day, and zinc or placebo syrup were given daily during diarrhea until 7 days after recovery. The placebo syrup (1 kg syrup contained 597 g of water, 400 g of sugar, 1.2 g of peach flavor number 061508 [Einar Willumsen, 23–25 Abildager, Brøndby, Denmark], 1 g of methylparabene, 1 g of xanthan gum, 0.15 g of saccharin sodium) and the zinc syrup were identical in appearance. The taste and acceptability of the syrup was assessed in Scandinavian and Indian adults and children before manufacture. The highest concentration at which the taste of the placebo and zinc syrups was identical was 2.5 mg of zinc per mL, although even additional dilution could not mask a minor metallic aftertaste. We administered 6 and 12 mL of syrup daily to infants and older children, respectively, to provide 3 RDAs of zinc. The capsules and syrup with backups were packed in separate plastic bags, which were assigned a unique serial number before it was shipped to Nepal. The randomization list that linked the serial numbers with the group identity was kept at the Statens Serum Institute in Copenhagen, Denmark, until the end of enrollment and follow-up. Whether the child belonged to the open “caretaker-zinc” group or to one of the blinded placebo, zinc, or zinc-vitamin A groups was not revealed to the study staff until after the child had been enrolled. This information was kept inside sealed envelopes in the individual plastic bags that were opened only after the vitamin A or placebo capsules were administered. In the placebo, zinc, and zinc-vitamin A groups, the syrup was administered daily by a field worker at home except on public holidays when the syrup was given by the caretaker, usually the mother. In the caretaker-zinc group, the caretakers were requested to administer the zinc syrup every day. Thus, the study staff and the caretakers in the open “caretaker-zinc” group knew that the children received zinc.

Oral rehydration salts packets were given to the mother with instructions on its mixing and administration, along with standard messages on feeding. Acute lower respiratory tract infections, dysentery, anemia, and severe malnutrition were managed according to World Health Organization guidelines.¹⁶

Fig 1. Profile of a randomized, placebo-controlled trial evaluating 3 RDAs of daily zinc administration as treatment for acute diarrhea in children 6 to 35 months of age.



Data Collection

Children were weighed at enrollment using a scale with 100 g sensitivity (Salter, SECA, Germany). A study physician drew blood from the cubital vein into zinc-free heparinized polypropylene tubes (Sarstedt, Nümbrecht, Germany) at enrollment and in a 15% random subsample after 14 days. Heparinized blood was centrifuged, separated, and transferred to zinc-free polypropylene vials (Eppendorf, Hinz, Germany) and kept frozen until analysis. The hemoglobin concentration was analyzed with Hemocue (Ängelholm, Sweden), and cases of anemia were treated with iron sulfate according to national guidelines. Plasma zinc was determined by inductively coupled plasma atomic emission spectrometry from Thermo (Jarell-Ash, Franklin, MA), at a wavelength of 206.2 nm.

We examined the child and recorded day-wise information on morbidity every fifth day until recovery from the diarrhea episode. At each visit, details of illness characteristics, including the number and character of stools and vomiting, on each day since the last visit were obtained, and hydration status was assessed.

Compliance was measured by reported intake and by measuring the remaining volume of syrup in the returned bottles. On a group level, delivery of zinc was assessed by average change in plasma zinc concentration from baseline. Field workers observed and recorded side effects such as regurgitation of the syrup during the first 15 minutes after administration. In the caretaker-zinc group, information on compliance, regurgitation, and vomiting was based on recall and recorded every fifth day on the morbidity visit. In addition, on the last day of supplementation when children were visited for bottle collection, the response to an open question about other side effects was recorded.

The field workers were trained until they reached the desired level of intra-observation and interobservation variability for measurement of respiratory rate, body temperature, height, and weight. They were also trained to memorize the standard messages to ensure uniformity of the information to the study participants. Retraining, standardization, and supervision of the field staff were done at 5 monthly intervals throughout the data collection period. Throughout the entire study period, in 8% of all home visits, supervisors or study physicians supervised the field workers or undertook independent visits, completing the same questionnaires in addition to a separate form on field worker performance. This was done to ensure appropriate interaction between the participants and the study staff and to maximize data quality.

Data Management and Analysis

The data were double entered into Microsoft VisualFoxPro databases (Microsoft Corp, Redmond, WA) with computerized logic, range, and consistency checks. If errors were detected, the forms were returned to the field for correction the next day. Weight-for-age, length-for-age, and weight-for-length *z* scores were calculated using LMS values¹⁷ obtained from Centers for Disease Control and Prevention growth charts.¹⁸ Statistical analyses were undertaken using the statistical, data management

package Stata, version 6 (StataCorp, College Station, TX) and SAS version 8.1 (SAS Institute, Cary, NC). All analyses were conducted on an intent-to-treat basis. The identity of the 4 intervention groups was revealed to the investigators only after the statistical analyses were completed. Log-transformed counts of the total number of stools during the first 4 days were compared between the groups using linear regression, values were antilogged, and the results were expressed as geometric mean or the ratios of geometric means compared with the placebo group.

Relative risks were obtained by a generalized linear model with binomial variability and a logarithmic link function. Comparison of the number of days from enrollment until recovery was undertaken using a Cox proportional hazards model with the "discrete" option in SAS for handling ties. We coded the outcomes and interventions so that ratios of geometric mean <1, relative risks <1, and hazard ratios >1 would represent a beneficial effect.

Correction for repeated entries of the same child was done by generalized estimation equations with an exchangeable covariance-variance structure corresponding to a random cluster effect.

RESULTS

Twenty-nine percent of the enrolled children were stunted and 22% wasted (Table 1). Infants constituted 41% and there were more boys (55%) than girls. The residence of the children was evenly distributed among the 17 administrative areas of Bhaktapur municipality. One hundred eighty-five children were enrolled twice, and 13 were enrolled 3 times.

Almost 10% reported blood in stools before enrollment and, when examined by the study physician, 12% were mildly dehydrated. We had few dropouts, which were evenly distributed among the study groups (Fig 1). Of the 14 children lost before recovery, 5 withdrew consent, and 9 migrated out of the study area.

Baseline characteristics, including the severity of disease, pre-enrollment duration, child and family characteristics, and baseline zinc concentrations were evenly distributed between the intervention groups (Table 1). More than 95% of the scheduled doses were reported to be consumed in all 4 groups; this was confirmed by measuring the remaining syrup on return of the bottles and reflected in the change in plasma zinc concentration (Table 2).

The mean duration of diarrhea was shorter and the proportion with duration more than 3, 7, and 14 days consistently and substantially lower among the chil-

TABLE 1. Enrollment Characteristics of 4 Groups of Children 6 to 35 Months of Age in a Trial Evaluating 3 RDAs of Daily Zinc Administration as Treatment for Acute Diarrhea

Variable	Study Group			
	Placebo	Zinc	Vitamin A-Zinc	Caretaker-Zinc
Mean age, mo	15.9 (7.9)	15.3 (7.6)	15.5 (7.8)	15.4 (7.9)
Percentage of infants	39.2	39.8	39.6	43.8
Percentage male gender	54.6	58.8	54.4	53.6
Percentage breastfed	81.4	82.8	83.6	83.7
Total number of stools 24 h before enrollment	8.8 (4.1)	9.0 (4.2)	9.2 (4.5)	8.8 (3.5)
Number of watery stools 24 h before enrollment	3.1 (4.1)	3.0 (4.0)	3.2 (4.2)	2.6 (3.8)
Percentage reporting blood in stool	12.1	10.7	8.4	7.8
Mean number of diarrhea days before enrollment	2.2 (1.2)	2.1 (1.2)	2.2 (1.1)	2.2 (1.1)
Percentage dehydrated	11.9	12.1	10.4	12.1
Percentage less than -2Z length for age (stunted)	29.5	29.1	31.3	27.9
Percentage less than -2Z weight for length (wasted)	23.3	21.5	23.8	20.3
Mean hemoglobin level (g/dL)	11.2 (1.1)	11.1 (1.1)	11.1 (1.3)	11.1 (1.3)
Percentage of mothers who can read	50.0	53.1	45.6	58.1
Percentage of fathers who can read	83.8	88.4	81.0	86.5
Average plasma zinc concentration (μmol/dL)	8.6 (1.4)	8.7 (2.2)	8.8 (1.5)	8.7 (1.9)

Standard deviation in parentheses; dehydration defined according to World Health Organization guidelines.

TABLE 2. Main Outcomes in a Trial Evaluating 3 RDAs of Daily Zinc Administration as Treatment for Acute Diarrhea in Children 6 to 35 Months of Age

Variable	Study Group			
	Placebo	Zinc	Vitamin A-Zinc	Caretaker-Zinc
Duration of supplementation (d)	10.6	9.9	10.0	10.0
Percent of days with scheduled syrup administration	98.2	97.6	97.1	95.8
Average daily zinc ingested by the infants (mg/kg/d)	0	1.9	1.9	1.9
Average daily zinc ingested by other children (mg/kg/d)	0	3.1	3.1	3.1
Mean plasma zinc ($\mu\text{mol/dL}$) change (SD)*	-0.2 (2.1)	3.7 (5.9)	4.6 (8.0)	2.7 (4.7)
Mean plasma copper ($\mu\text{mol/dL}$) change (SD)*	-1.5 (4.2)	-1.1 (5.5)	-1.4 (4.1)	-1.8 (4.5)
Relative hazard (time to recovery)	1	1.26 (1.08,1.46)	1.21 (1.04,1.38)	1.19 (1.02,1.40)
Risk Ratios or Ratios of Geometric Mean Compared With Placebo (95% CI)				
Cases (%) with postenrollment duration >3 d	159 (35.7)	0.75 (0.61,0.91)	0.83 (0.68,1.00)	0.80 (0.66,0.97)
Cases (%) with postenrollment duration >7 d	58 (13.1)	0.57 (0.38,0.86)	0.53 (0.35,0.81)	0.55 (0.37,0.84)
Cases (%) with postenrollment duration >14 d	11 (2.5)	0.55 (0.20,1.47)	0.64 (0.25,1.63)	0.64 (0.25,1.63)
Cases (%) with postenrollment watery diarrhea	167 (37.6)	0.91 (0.76,1.08)	0.90 (0.76,1.08)	1.03 (0.87,1.21)
Geometric mean number of stools first 4 d (95% CI)	13.9 (13.2,14.6)	0.91 (0.85,0.97)	0.95 (0.89,1.02)	0.93 (0.87,1.00)

SD indicates standard deviation; CI, confidence interval.

* Change from enrollment until 14 days thereafter.

dren in the zinc, vitamin A-zinc, and caretaker zinc groups than in the placebo group (Table 2). The hazard ratios between the placebo group and the intervention groups were 1.26, 1.21, and 1.19, respectively. The proportion with prolonged diarrhea was 43%, 47%, and 45% lower in these 3 groups (Table 2) compared with placebo. Only 2.5% of the episodes in the placebo group lasted >14 days after enrollment. The effect sizes at this cutoff were similar to what was seen at day 7, but with wider confidence intervals, which included 1 (Table 2).

Daily average stool frequency during the first 4 days after enrollment was marginally lower in children that received zinc (Table 2). The proportion of cases with watery diarrhea after enrollment in the children receiving zinc was not substantially or significantly different from those receiving placebo (Table 2).

There was no difference among the 3 groups of children that received zinc in the severity, as measured by stool frequency, or in the duration of diarrhea (Table 2).

Other Effects

A higher proportion of syrup administrations was followed by regurgitation in the children receiving zinc than in those receiving placebo (Table 3). In the placebo group, 1.3% of the administrations were followed by regurgitation while this percentage was 5.0%, 5.1%, and 7.3% in the zinc, vitamin A-zinc, and caretaker zinc groups, respectively. The figures in Table 3 give the percentage with regurgitation on the first day and on the subsequent days separately. Approximately one third of these regurgitations occurred on the enrollment day regardless of group identity. The excess regurgitation in children given zinc was similar in the different age groups (Table 3). The total vomiting beyond the 15 minutes after syrup administration was also higher in the children receiving zinc (Table 3).

An open question asked on the last day of supplementation revealed no other side effects than vomiting or regurgitation, nor were any such adverse events observed during the intervention period. The change in plasma copper was the same in children receiving zinc as in children receiving placebo (Table 2).

Eight hundred thirty-two of the enrolled children made 1209 visits to the field clinic; the number of visits and the number of children who visited the field clinic were similar among the intervention groups. Likewise, there were no differences in caretaker-reported morbidity, the number of physician visits, or hospitalizations during the 1-month period after recovery from the diarrhea episode.

DISCUSSION

Our data show a substantial and highly significant beneficial effect of zinc on the duration of diarrhea in children between 6 and 35 months of age. We enrolled children from an entire Nepalese urban area, and the recruitment was not restricted to a slum or to selected patient groups. This is in contrast to previous reports where inclusions were limited to lower socioeconomic strata, hospitalized, or to malnourished children.¹⁻⁷ The overall effect size in the present study was larger than what has previously been reported. Thus, in our study, zinc resulted in a 43% to 47% reduction in the risk of prolonged diarrhea. This impact is similar to what was found in the subgroup of children enrolled by day 3 after onset of diarrhea in a trial in a New Delhi slum.¹ We included only children who had had diarrhea for 4 days or less, suggesting that zinc is more effective when given early in the course of the illness.

Although we demonstrated a reduction in daily total stool frequencies, this effect was of much smaller magnitude than that on duration. The most important effect of zinc is probably to prevent a nutritional insult caused by persistence of the epi-

TABLE 3. Regurgitation of Syrup and Vomiting Among Children 6 to 35 Months of Age in a Trial Evaluating 3 RDAs of Daily Zinc Administration as Treatment for Acute Diarrhea

Variable	Study Group			
	Placebo	Zinc	Vitamin A-Zinc	Caretaker-Zinc
Percentage of children with syrup regurgitation on enrollment day	6.1*	18.6*	21.0*	24.4
Risk ratios (95% CI)	1	3.1 (2.0,4.7)	3.6 (2.4,5.4)	4.0 (2.7,6.0)
Infants	4.6	16.9	20.9	23.6
Risk ratios (95% CI)	1	3.7 (1.7,7.8)	4.6 (2.2,9.5)	5.2 (2.5,10.6)
Older than 12 mo	7.0	19.7	21.1	25.1
Risk ratios (95% CI)	1	2.8 (1.7,4.6)	3.0 (1.8,4.9)	3.6 (2.2,5.8)
Percentage of days with syrup regurgitation after inclusion day	0.9*	3.8*	3.8*	5.8
Risk ratios (95% CI)	1	4.3 (2.8,6.6)	4.0 (3.1,5.1)	5.6 (4.4,7.2)
Infants	1.0	3.9	4.1	6.2
Risk ratios (95% CI)	1	3.9 (2.5,6.1)	4.0 (2.6,6.34)	6.1 (4.0,9.4)
Older than 12 mo	0.8	3.7	3.6	5.5
Risk ratios (95% CI)	1	4.4 (2.9,6.7)	4.3 (2.8,6.5)	6.6 (4.4,9.9)
Percentage of children with reported vomiting on enrollment day	18.9	32.7	37.1	38.8
Risk ratios (95% CI)	1	1.7 (1.4,2.2)	2.0 (1.6,2.5)	2.1 (1.6,2.6)
Percentage of days during diarrhea with vomiting after enrollment day	8.7	16.0	17.3	17.9
Risk ratios (95% CI)	1	1.8 (1.42,2.45)	2.0 (1.6,2.6)	2.0 (1.5,2.6)

CI indicates confidence interval.

* Children were observed for regurgitation and other adverse effects for 15 minutes after a field worker had given the zinc or the placebo syrup.

sode and not to reduce the risk of severe dehydration,¹⁹ and should therefore be considered as an important addition to oral rehydration therapy.

This trial demonstrates that zinc is as effective in treating diarrhea when given daily by the caretaker as when given by trained field workers. In our population, the effect was not restricted to children who were also given vitamin A, nor was it enhanced by vitamin A administration at enrollment, although the power to identify the latter was limited. This indicates that zinc exerts its beneficial effect independently of vitamin A. Indeed, the results from studies of the effect of vitamin A on the recovery from acute diarrhea are conflicting.^{11,20–22}

The compliance in the caretaker zinc (effectiveness) group may have been reinforced by the morbidity visits. However, the field workers were requested to restrain from message delivery during these visits and the effectiveness of zinc was evident already on the third day after enrollment (Table 2), ie, even before the first morbidity visit.

Zinc-supplemented children experienced more regurgitation and vomiting than did children who received placebo. Regurgitation and vomiting have not previously been reported as a side effect of zinc when treating diarrhea. Our findings may be attributable to the fact that our dose was relatively high compared with many other trials, and that in some of these trials, the daily dose was divided.^{3,4,7} On the other hand, it could also be a reflection of more careful monitoring, as adverse effects were one of the study outcomes. One third of the regurgitation after syrup ingestion occurred on the first day. In addition to the fact that the children may have been somewhat stressed in the field clinic, a more careful dispensing by the field workers or caretakers or gastrointestinal adaptation to zinc may explain the lower regurgita-

tion frequency on the subsequent days. The observed regurgitation and vomiting did apparently not interfere with the oral rehydration therapy, nor was zinc supplementation associated with dehydration (data not shown). If zinc is to be used routinely in acute diarrhea, adjustment or division of the daily dose, or perhaps mixing zinc with the oral rehydration salts solution, could increase acceptance and thereby secure a high effectiveness under program conditions. Other trials suggest that a lower daily zinc dose may be almost as efficacious^{1,3,5} with seemingly no excess vomiting or regurgitation, although the registration of side effects may have been less rigorous than in our study. Therefore, a daily dose of 2 RDAs may be advisable. Copper status may be affected by zinc administration¹⁵; plasma copper levels were not influenced by the short term therapeutic zinc administration of our study.

We were not able to demonstrate any differences in morbidity among the study groups during the 1-month follow-up period after recovery. Thus, any beneficial effect of zinc supplementation beyond the episode was not identified, nor did we reveal any increased morbidity in the children who received zinc.

No other treatment has been proven as efficacious as zinc in reducing the duration of acute diarrhea in children of developing countries. Antibiotics, antiparasitic, antimotility, and antisecretory drugs and gastric enzymes are overused. Zinc is efficacious and, in this trial, despite some increase in regurgitation and vomiting, effective and safe in the treatment of diarrhea. If promoted as an integral part of the routine management of acute diarrhea instead of the above mentioned inefficacious and potentially harmful remedies, the promotion of oral rehydration therapy may be strengthened and the spread of antibiotic

resistance limited. A substantial proportion of diarrheal deaths occur in prolonged diarrhea.^{19,23} Decreasing the occurrence of prolonged and persistent diarrhea by zinc administration may substantially reduce the number of childhood diarrhea deaths.

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