Journal of Pediatric Gastroenterology and Nutrition
42:300–305 © March 2006 Lippincott Williams & Wilkins, Philadelphia

Zinc Supplementation in Acute Diarrhea is Acceptable, Does Not Interfere with Oral Rehydration, and Reduces the Use of Other Medications: A Randomized Trial in Five Countries

INCLEN Childnet Zinc Effectiveness for Diarrhea (IC-ZED) Group

ABSTRACT

Objective: Assess the impact of zinc supplementation with locally developed culturally specific educational statements (messages) on oral rehydration solution (ORS) and antibiotics or antidiarrheal use in children with acute watery diarrhea as well as to assess adherence and side effects of zinc.

Methods: This was a randomized effectiveness trial conducted in outpatient health facilities of six sites in five countries, namely, Fortaleza (Brazil), Addis Adaba (Ethiopia), Cairo (Egypt), Lucknow and Nagpur (India), and Manila (Philippines). Participants were 2,002 children aged 2 to 59 months. Intervention was zinc (20 mg orally, once daily for 14 days) with ORS (zinc group) compared with ORS alone (control group). Primary outcomes were ORS use on day 3 to 5; adherence to zinc; and any use of an antibacterial/antidiarrheal up to day 14.

Results: One thousand ten and 992 children enrolled in zinc and control groups, respectively. Loss to follow-up on days 3 to 5 and 15 to 17 was 1.2% and 2.8% in the zinc group and 0.8% and 1.7% in the control group. In five of six sites, ORS use in cases with continued diarrhea on days 3 to 5 was the same in the two groups or higher in zinc group. Overall adherence to zinc supplementation was 83.8% (95% confidence interval [CI] 81–86). There was no difference in vomiting by group. In consideration of the six countries overall, less antibiotic/antidiarrheal use occurred in the zinc group (absolute difference, 3.8% [95% CI 1.7–5.9]).

Conclusions: In the management of acute watery diarrhea, zinc plus ORS along with culturally appropriate, site-specific messages in local language does not affect overall ORS use generally and decreases antibiotic/antidiarrheal use; children had good adherence without side effects. ***JPGN 42:300–305, 2006.***

Key Words: © 2006 Lippincott Williams & Wilkins

Oral rehydration solution (ORS) has been successfully used around the world and has been responsible for reduction in diarrheal deaths in the last 2 decades (1). In spite of the success of ORS in prevention of dehydration, there is still a demand for medicines that will reduce the duration and severity of diarrhea. Consequently, many cases are treated with antibiotics and other drugs (2). Zinc has been shown to be efficacious in reducing the duration of diarrhea (3–9) and associated mortality (11–12). In Bangladesh, the provision of zinc supplements for use during diarrhea by a village-based worker who also gave ORS increased the use of ORS (13) and decreased the use of antibiotics and other drugs (13). It is critical to ensure in other settings that any promotion of zinc for treatment of diarrheal disease does not interfere with the use of ORS; in addition, it would be desirable to reduce the use of drugs for diarrheal disease. Therefore, we conducted this study with the hypothesis that zinc supplementation during acute watery diarrhea will not affect use of ORS, that it will reduce the use of antimicrobial and antidiarrheal drugs, and that zinc supplements will be accepted for treatment. The study also aimed to develop culturally appropriate educational statements (messages) for promotion of the use of zinc during and for a short period after diarrhea.

Received October 18, 2004; accepted June 27, 2005.

Address correspondence and reprint requests to Dr. Shally Awasthi, Department of Pediatrics and Clinical Epidemiology, King George's Medical University, Lucknow (UP)-226003, India. (e-mail: sawasthi@sancharnet.in).

METHODS

Setting

This study was conducted after institutional ethical clearances had been obtained in outpatient health facilities of Fortaleza (Brazil), Addis Adaba (Ethiopia), Cairo (Egypt), Lucknow and Nagpur (India), and Manila (Philippines).

Population

All children aged 2 to 59 months presenting to the study centers with diarrhea, defined as three or more loose or watery motions per day (14), and of less than 7 days' duration, were invited to participate. Excluded were those with severe malnutrition (weight for height z score [WHZ] < -3 SD), on zinc supplementation, on World Health Organization (WHO) Plan B or C for management of dehydration (14), with dysentery, needing hospitalization of more than 12 hours for the current episode of diarrhea, whose mothers reported a positive HIV status, currently using antimicrobial drugs, having other conditions requiring antimicrobials, not residing in catchment area, or whose parents/guardians did not consent to participate.

Sample Size Calculations

Sample size calculations were based on the reported use of oral rehydration therapy (ORT) and drugs for acute diarrheal disease in the National Family Health Survey performed in India 1998 to 1999 (15). With use of the reported 50% ORT use and assuming a 10% difference would be the smallest difference of clinical interest, the required sample size of 392 per group was needed to test equivalence in zinc plus ORS (zinc group) and ORS group (control group). A similar sample size was needed for antibiotic/antidiarrheal usage rate. The sample size required to assess adherence to the zinc therapy, if the resulting estimate were to fall within 7% points of the true proportion with 95% confidence and assuming the true proportion to be 50% (a conservative estimate in the sense that sample variation would then be at a maximum), is 196 in the zinc group only. To take into account 5% loss to follow-up and to ensure that each site had adequate numbers for assessment of adherence, 200 subjects per group were to be recruited by each center over a period of 9 to 12 months. Thus, the total study sample would be 1,200 in each group. This sample size was thought to be adequate to measure primary outcomes, including changes if any in the antibiotic/antidiarrheal usage rate, taking into account the clustering effect associated with randomization by day.

Randomization

A blocked randomization procedure was used for each site using block of size 4. The unit of randomization was day. On a particular day, all the recruited patients received either zinc and ORS or ORS alone. The number of subjects to be recruited at each site was limited to maximum of five each day; this was to reduce the potential loss of precision in the results associated with the clustering of the observations by day within centers. The randomized assignments to intervention groups were performed at the coordinating center and transmitted to different sites using a set of sealed, numbered envelopes.

Intervention

This was an effectiveness trial. Therefore, there were no other interventions that may have affected outcomes through the project activities. While subjects randomized to both the groups received instructions for the use of ORS, those randomized to the zinc group also received zinc tablets along with counseling and site-specific, culturally appropriate messages for zinc usage. Message development was a critical component of the effectiveness trial. It was essential that zinc promotion did not compete with the ORT message and that zinc be seen as a complement and not a replacement for ORT. Promoting adherence to the zinc regimen once an episode of diarrhea abated constituted a significant challenge. Messages were designed to include both a diarrhea-specific curative message and a preventive health message associated with diarrhea or a health concern afforded importance by mothers in different cultures. Formative research was conducted to identify culturally appropriate messages at each site (16). The formative research process involved a review of the existing literature on diarrheal disease-related behavior in each region; an assessment of existing ORT messages and a content analysis of advertisements for popular diarrhea medicines in the marketplace; key informant interviews exploring mothers' health concerns related to diarrhea disease management, convalescence, and prevention; focus groups designed to generate and select culturally appropriate zinc messages; a behavioral trial to pretest messages before use in the main trial; and exit interviews with mothers after the completion of their child's treatment to document perceived benefits of zinc and the extent to which these benefits corresponded with initial zinc messages. Exit interviews provide data useful for future efforts to refine zinc messages in each site.

Zinc (Nutriset; manufactured by Rodael, Malaunay, France) as well as ORS was provided by WHO. Zinc was supplied as dispersible 10-mg tablets. Duration of zinc supplementation was 14 days. Ethiopia and Lucknow, India gave two zinc tablets, whereas the other sites gave one zinc tablet once per day because there were concerns about adherence to intake of two tablets per day by small children by care providers. Parents were instructed to dissolve zinc tablets in 5 mL clean water. In Philippines, Egypt, and Nagpur, India, they were also given instructions for dissolving it in breast milk and in the Philippines for dissolving in ORS as an option.

Patient Assessment and Follow-Up

Baseline characteristics were recorded for eligible children. All caretakers were trained to recognize the signs of worsening illness as outlined in the WHO diarrhea manual and advised to report to the hospital immediately if any of these signs developed. Caregivers were asked to come for two follow-up visits, the first between days 3 and 5 and the second between days 15 and 17, bringing with them any unused ORS packets and zinc tablets. They were also instructed to retain the wrappers, bottles, and prescriptions of all medicines used during the current diarrheal episode and requested to bring these at follow-up visits. A project nurse visited the homes of the patients within 6 hours if the child was not brought to the hospital by noon on the expected day for each follow-up visits.

Outcome Measures

Primary outcome measures were (1) ORS use on first follow-up visit, defined as use of ORS in last 24 hours if the child had diarrhea, (2) adherence to zinc tablets, defined as consumption of greater than 80% of the doses and assessed by pill count on follow-up days, and (3) any use of antimicrobial/antidiarrheal drug up to day 14. Secondary outcome measures were frequencies of possible adverse effects of zinc, namely vomiting, and of treatment failures, defined as one or more of the following after institution of therapy: dehydration, need for intravenous fluids, hospitalization, death.

Data Analysis

The data collected at all the six sites were transferred to the coordinating center, where double data entry was performed. The primary analysis was performed on an intention to treat basis (17). All the analyses were stratified by center, and overall estimates of effect size were obtained by pooling the results across the centers. Breslow-Day test was used to study the interaction of effect size across different centers. We

compared baseline and other characteristics, ORS use, and drug use between the two treatment groups. We used the chi-square test for categorical variables and Student's *t*-test for continuous variables. The tests of significance and confidence intervals (CI) for primary outcome measures were performed taking into account the cluster (day) effect. Subgroup analyses were preplanned and were performed by the primary outcomes sex and age of the child, malnutrition status, and number of tablets used per day.

RESULTS

The messages used for each site are given in Table 1 (translated to English). The number of days randomized and the number of children recruited in each arm of the trial is given in Figure 1 in the format recommended by the CONSORT statement (18). There were 1,010 and 992 children in the zinc and control groups. Loss to follow-up on days 3 to 5 and 15 to 17 were 1.2% and 2.8% and 0.8% and 1.7% in zinc and control groups, respectively.

Baseline Characteristics

Although there was substantial variability among sites, the baseline characteristics of subjects in each site were comparable in the two groups (Table 2). Subjects in Egypt had the shortest duration of illness because the study was conducted in the primary health care setting, and mothers usually reported immediately after onset of diarrhea.

Outcome Measures

Overall adherence was 83.8% (cluster [day] effect adjusted 95% CI, 81–86) and was greater than 75% at all sites. At first follow-up, on days 3 to 5, 22.3% (n = 225) of children in the zinc group versus 26.2% (n = 260) in the control group still had diarrhea ($P = 0.04$). In those who had diarrhea on days 3 to 5, overall ORS use was 85.3% (n = 192) and 86.1% (n = 224) in zinc and control groups, respectively (absolute difference 0.8% [95% CI −5.−5–7.1]). In five of six sites, ORS use was the same in the two groups or tended to be higher in the zinc group. However, in Brazil, the use of ORS in those randomized to the zinc group was 68.8% versus 89.2% in the control group (Table 3). In considering all the six sites, any antimicrobial/antidiarrheal drug use was lower in the zinc group compared with the control group (4.1% vs. 7.9%; absolute difference 3.8% [95% CI 1.−6 to −6.0]).

On days 3 to -5, vomiting was reported in 8.6% in the zinc group versus 6.8% in the control group, and on day 15 to 17, this symptom was reported, respectively, in 1.4% versus 0.7%. Absolute difference on days 3 to 5 was 1.8% (95% CI −0.5–4.2) and on day 15 was 0.7% (95% CI −0.2–1.6). Clinical failures were 1.8% in zinc group and 2.9% in control (absolute difference 1.1% [95% CI −0.2–2.4]). Combining both groups, there were 2.2% (n = 44) cases of dehydration, 1.6% (n = 32) cases of intravenous fluids, 0.6% (n = 12) hospitalizations, and one death (unrelated to diarrhea).

During the study duration, there were 137 children who went to seek care in other facilities, 41 (4%) in the zinc group and 96 (9.7%) in the control group (absolute difference 5.7%,

TABLE 1. *List of messages used by sites (to be filled by sites)*

	Country	Message (in English and local language)
1	Brazil	Zinc tablets for the treatment of children with diarrhea increases the child's resistance and appetite and it is a vitamin for intestine recuperation "*Para tratamento de criancas com diarreia para aumentara resistencia da crianca aumentaro appetite, vitamina para recuperar o intestino da crianca*"
2	Ethiopia	Drug that prevents the child from getting sick again "*Endegena bebeshetaw Endayeteka Yadergal*" Drug that prevents diarrhea from becoming worse "*Tekematu endayebabas yadergal*" Drug that increases the resistance of a child with diarrhea "*Beshita yemekelakel akim yechemiral*"
3	Egypt	The medicine will Decrease the duration of diarrhea Decrease the number of motions during diarrhea episode Prevent diarrhea episode from getting worse Increase appetite of a child with diarrhea "*YeKalel Modet El-eshaal.* "*Yemnaa Tadahwr Helt El-eshaal*" "*Yehasen Shaheit El-tifl*"
4	India (Nagpur)	Zinc when given with ORS Reduces the severity and duration of diarrhea and prevents recurrence Increases the appetite of the child *Jehavan jhinkhi goli watai powder sobat dili jate* "*Atisari tivarta kami hote aadi*" "*Atisari kalavadhi pad kami hote aadi*" "*Atisari punah hodyapasun bachaav karto*" "*Mulanchi bhookh suudata vadhvato*"
5	India (Lucknow)	14 days of zinc supplementation will Cure this episode of diarrhea as well as prevent future episodes of diarrhea Make sure that child is fully recovered from this episode of diarrhea "*Chaudah din tak zaste ka istamal is dast ko to dheek kare ga hi varan age hone ki sambhavao ko bhi kam kare ga*"
6	Philippines	Zinc increases the appetite of child with diarrhea Zinc strengthens the resistance of child with diarrhea Zinc is a vitamins for the gut of a child with diarrhea "*Gamot na pampagana pag nagtatae ang bata*" "*Gamot na pampatibay ng resistensya ng batang nagtatae*" "*Bitamina para sa tiyan ng batang nagtatae*"

ORS, oral rehydration solution.

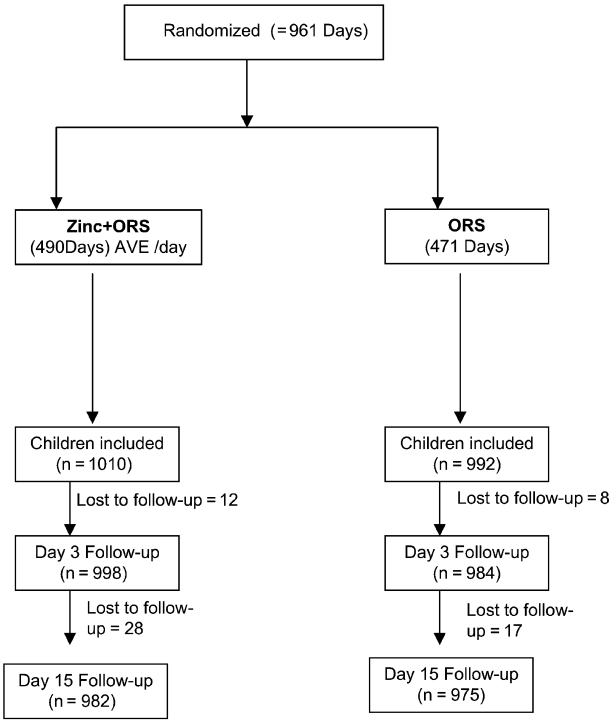

FIG. 1. CONSORT statement for trial.

95% CI 3.5–7.9%; $P < 0.001$). Home visits were made for follow-up for 1,033 children, of which 479 (47.0%) were in the zinc and 554 (55.8%) in the control group.

On subgroup analysis for the primary outcomes, adherence to the zinc protocol was very similar in boys and girls. Adherence was slightly lower in infants below 1 year of age, in malnourished children (WHZ score below −1 SD), and in centers where two tablets per day had been used (Ethiopia and Lucknow); these subgroup differences were approximately 2%, but none was statistically significant. Rates of ORS use on day 3 and of antimicrobial/antidiarrheal use up to days 3 to 5 and 13 to 15 did not vary significantly by subgroup.

CONCLUSIONS

This randomized, open-label effectiveness trial was conducted at six sites in five developing countries. There was excellent adherence to zinc supplementation during and for a short period after diarrhea and no difference in vomiting between the groups on days 3 to 5. We found that 15% fewer ($P = 0.04$) children in the zinc group than the control group had continuation of diarrhea to days 3 to 5, which is consistent with the shortening of duration of diarrhea with zinc found in many placebo-controlled trials (3–10). There were 37.9% fewer clinical failures by days 3 to 5 in children randomized to the zinc group compared with the control group, but the difference was not statistically significant ($P = 0.09$).

The primary hypothesis in this study was that supplementation with zinc along with ORS would not affect the use of ORS, and this was true overall and in five of six sites. The reasons for the lower ORS use in the zinc-treated children in Brazil are not known, and further formative research is needed in this site to determine how to promote zinc so that it does not detract from ORS use.

The impact of the use of zinc on the purchase and use of antimicrobial and antidiarrheal drugs is of great interest in that these drugs are unnecessary and can be costly and hazardous. These findings of a reduced rate of drug use in the zinc group are similar to the community trial from Bangladesh, except that in our trial, the frequency of drug use was relatively low, probably because of the exclusion of children taking such drugs from the study and counseling against drug use in both zinc and control groups (13).

The current trial was performed in low and middle-income settings with a high prevalence of diarrhea (19). Included were children who chose to attend the health facilities; therefore, the results are generalizable to such settings elsewhere. This extends the evidence for safety and benefit of zinc used along with ORT for the management of diarrhea and includes countries without prior trial experience similar to those participating in this study. After this multicenter trial was begun, WHO and UNICEF issued new guidelines for management of diarrhea, including the recommendation that zinc supplements be given in all episodes along with fluid replacement and continued feeding (20). Results of this trial indicate that these recommendations can be confidently implemented in diverse settings. In doing so, formative research is critical to shape messages and

TABLE 2. *Baseline comparability by site*

Site	Brazil	Ethiopia	Egypt	Nagpur	Lucknow	Philippines
n	400	248	401	400	415	138
Age (mo), mean, SD	20.2, 14.6	12.9, 9.7	17.0, 12.6	17.9, 13.3	17.7, 13.5	14.2, 11.5
Sex, female (%)	43	46	46	47	42	46
Weight for height, 2 to -3 SD, %	2.3	10	0.7	28	23	9
Duration of illness, mean, SD	3.0, 1.4	3.7, 2.0	1.2, 0.6	2.4, 1.5	2.9, 1.7	2.7, 1.2
Vomiting (%)	56	71	37	36	18	49
Breastfed children ≤ 12 mo (n/N, %)	79/159, 50	124/153, 81	203/210, 97	172/184, 94	132/212, 63	28/83, 34
Uneducated mothers (n/N, %)	383/400, 96	241/245, 98	400/400, 100	365/400, 91	344/415, 83	137/137, 100

TABLE 3. *Primary outcome measure: oral rehydration solution (ORS) use on day 3 among patients with diarrhea*

	ORS use		
Site	Zinc + ORS n/N, %	ORS n/N, %	Absolute difference, CI
Brazil	22/32, 68.8	33/37, 89.2	20.4 (0.8, 40.1)
Ethiopia	35/50, 70.0	38/56, 67.9	2.1 (−15.7, 20.0)
Egypt	29/29, 100.0	62/63, 98.4	1.6 (−1.5,4.7)
Nagpur	72/77, 93.5	56/62, 90.3	3.2 (−6.0, 12.4)
Lucknow	31/34, 91.2	28/33, 84.8	6.3 (−9.7,22.4)
Philippines	3/3, 100.0	7/9, 77.8	22.2 (−6.6,51.0)
Overall	192/225, 85.3	224/260, 86.2	0.8 (−5.5,7.1)

Breslow Day Statistics: $\chi^2 = 6.8$, $P = 0.23$.

communication strategies to ensure culturally appropriate promotion of zinc as an adjunctive therapy for diarrhea.

Acknowledgments: Dr. Maryke Funk, Consultant Pediatrician Pretoria Academic Hospital, Pretoria, South Africa, participated in protocol development. Dr. Deepak Jain, KG Medical University, assisted in manuscript writing.

INCLEN Childnet Zinc Effectiveness for Diarrhea (IC-ZED) Group

List of Investigators (in alphabetic order): Shally Awasthi, Department of Pediatrics and Institute of Clinical Epidemiology, King George Medical University, Lucknow, India

Antonio da Cunha, Department of Pediatrics and Clinical Epidemiology Unit, Rio de Janeiro, Brazil

Leonila F. Dans, Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines, Manila, Philippines

Hesham Fathey El Sayed, Department of Pediatrics, Suez Canal University, Ismailia, Egypt

Germana V. Gregorio, Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines, Manila, Philippines

Dipti Jain, Department of Pediatrics, Govt. Medical College Nagpur, India

Sileshi Lulseged, Clinical Epidemiology Unit, Addis Ababa, Ethiopia

Alvaro Madeiro, Clinical Epidemiology Unit, Fortaleza, Brazil.

Project Coordinator: Dr. Shally Awasthi, INCLEN Childnet coordinator, Professor, Department of Pediatrics and Institute of Clinical Epidemiology, KG Medical University, Lucknow (UP), India 226003.

Members Central Coordination Team: Awasthi Shally, Paediatrician and Epidemiologist, Lucknow, India

Awarwal Girdhar, Biostatistician, Lucknow, India

Dr. Cecilia Acuin, Anthropologist, Manila, Philippines

Mr. Jaideep Singh, Computer Programmer, Lucknow, India

Ms. Tuhina Verma, Sociologist, Lucknow, India

Mr. Siddharth Roy, Biostatistician, Lucknow, India.

Technical Advisers: Professor Robert Black, Department of International Health, Johns Hopkins Bloomberg School of Public Health University, Baltimore, MD

Dr. Olivier Fontaine, Department of Child and Adolescent Health and Development (CAH), WHO, Geneva, Switzerland

Professor Stephen Walter, Department of Clinical Epidemiology and Biostatistics, Health Sciences Center, McMaster University, Hamilton, Canada

Professor Mark Nichter, Department of Anthropology, University of Arizona, Tucson, AZ.

Funding Agencies: USAID-CHR, Washington (via INCLEN Trust) Protocol development, project coordination and dissemination

USAID-Indian Mission Indian Infectious Disease Initiative Indian sites (Lucknow, Nagpur) project coordination and dissemination

Johns Hopkins' Family Health and Child Ethiopia and Egypt Sites

Survival Cooperative Agreement with USAID World Health Organization-CAHD Brazil and Philippines sites.

Biostatistician: Girdhar Agarwal, Lucknow University, Lucknow, India.

Social Scientists: Cecilia S. Acuin, Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines, Manila, Philippines

Alberta S. Vargas, Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines, Manila, Philippines.

Officer-in-Charge Randomization: Agarwal Girdhar, Lucknow University, Lucknow, India.

REFERENCES

1. Cleason M, Merson MH. Global progress in the control of diarrheal diseases. *Pediatr Infect Dis J* 1990;9:345–55.
2. Yudkin JS. Dispensing of inappropriate medicines for diarrhea. *Lancet* 1990;335:803.
3. Black RE. Therapeutic and preventive effects of zinc on serious childhood infectious diseases in developing countries. *Am J Clin Nutr* 1998;68(Suppl):476S–9S.
4. Sachdev HPS, Mittal NK, Mittal SK, Yadav HS. A controlled trial on utility of oral zinc supplementation in acute dehydrating diarrhea in infants. *J Pedia Gastroenterol Nutr* 1988;7:877–81.
5. Sazawal S, Black RE, Bhan MK, Ghandari N, Sinha A, Jalla S. Zinc supplementation in young children with acute diarrhea in India. *N Engl J Med* 1995;333:839–44.
6. Faruque AS, Mahalanabis D, Haque SS, Fuchs GJ, Habte D. Double blind, randomized, controlled trial of zinc or vitamin A supplementation in young children with acute diarrhea. *Acta Paediatr* 1999;88:154–60.
7. Roy SK, Tomkins AK, Akramuzzaman SM, Haider R, Mahalanabis D, Fuchs G. Randomized control trial of zinc supplementation in malnourished Bangladeshi children with acute diarrhea. *Arch Dis Child* 1997;77:196–200.
8. Sazwal S, Black RE, Bhan MK. Efficacy of Zinc supplementation in reducing the incidence and prevalence of acute diarrhea: a

community based, double blind, controlled trial. *Am J Clin Nutr* 1997;66:413–8.
9. International Center for Diarrheal Disease Research, Dhaka, Bangladesh. Zinc supplementation in the treatment of childhood diarrhea. *Indian J Pediatr* 1995;62:181–93.
10. Fuchs GJ. Possibilities of zinc in the treatment of acute diarrhea. *Am J Clin Nutr* 1998;68(Suppl):480S–3S.
11. Bhan MK, Bhandari N. The role of zinc and vitamin a in persistent diarrhea among infants and young children. *J Pedia Gasrtenterol Nutr* 1998;26:446–53.
12. Zinc Investigators' Collaborative Group. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. *Am J Clin Nutr* 2000;72:1516–22.
13. Baqui AH, Black RE, Arfeen SE, et al. Effect of Zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: Community Randomized Trial. *Br Med J* 2002;325:1059–63.
14. Division of Diarrheal and Acute Respiratory Disease Control. *The treatment of diarrhea: a manual for physicians and other senior health workers*. WHO/CDR/95.3. Geneva: World Health Organization: 1995.
15. *National Family Health Survey-2 (NFHS-2) INDIA1998-99. Child morbidity and treatment*. Mumbai: Diarrhea International Institute of Population Sciences, 2000:220–9.
16. Nichter M, Acuin CS, Vargas A. Introducing zinc in a diarrheal control program: a manual for conducting formative research. *International Network of Clinical Epidemiology Website*. Available at: http://www.inclentrust.org/downloads/zinc_manual_02_21_05.doc.
17. Norman GR, Streiner DL. *Biostatistics: The Bare Essentials*. St. Louis: Mosby Year-book, Inc., 1994:6–21.
18. Moher D, Schulz KF, Altman DA, for the CONSORT group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *Lancet* 2001;357:1191–94.
19. Sandstead HH. Is zinc deficiency a public health problem? *Nutriton* 1995;11:87–92.
20. WHO, UNICEF. *WHO-UNICEF Joint Statement on the Clinical Management of Acute Diarrhea*. Geneva: World Health Assembly, 2004.