Effect of Zinc Supplementation on Clinical Course of Acute Diarrhoea

Report of a Meeting, New Delhi, 7-8 May 2001

This report was drafted by the following persons on the occasion of a meeting held in New Delhi, India, on 7-8 May 2001: R. Bahl, New Delhi, India; A. Baqui, Baltimore, USA; M.K. Bhan, New Delhi, India (Chairman); S. Bhatnagar, New Delhi, India; R.E. Black, Baltimore, USA; A. Brooks, Dhaka, Bangladesh; L.E. Cuevas, Liverpool, United Kingdom; P. Dutta, Calcutta, India; R. Frischer, Washington, DC, USA; S. Ghosh, New Delhi, India; S. Malhotra, New Delhi, India; M. Penny, Lima, Peru; S.K. Roy, Dhaka, Bangladesh; H.P.S. Sachdev, New Delhi, India; D.A. Sack, Dhaka, Bangladesh; S. Sazawal, Baltimore, USA; T. Strand, Bergen, Norway; and the following members in the WHO Secretariat: O. Fontaine (Secretary), A.K. Patwari, N. Raina (Department of Child and Adolescent Health and Development, Geneva and SEARO), and Sultana Khanum (Department of Nutrition for Health and Development, SEARO)

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Effect of Zinc Supplementation on Clinical Course of Acute Diarrhoea

Abstract

This report summarizes the current knowledge on the effects of zinc supplementation on the management of acute diarrhoea. All published and unpublished studies on this topic, conducted in hospitals and in the community, were reviewed. Based on the results of this review, it is concluded that there is now enough evidence demonstrating the efficacy of zinc supplementation on the clinical course of diarrhoea, with regard to the severity and duration of the episode. However, the meeting also concluded that effectiveness studies to assess the feasibility, sustainability, and cost-effectiveness of different strategies for delivering zinc supplementation should be undertaken.

Key words: Zinc deficiency; Zinc; Diarrhoea, Acute; Nutrition; Impact studies

BACKGROUND

Over the past decade, substantial progress has been made in understanding the significance of nutrition in child health and survival, particularly the role of specific micronutrients in preventing childhood morbidity and mortality. Vitamin A, for example, was initially recognized for its role in preventing blindness. Its effects on the prevention of severe infections and deaths in children were identified in the early 1980s and confirmed through large trials in the decade that followed. More recently, findings of research suggest that zinc may be another micronutrient that can substantially decrease morbidity and mortality when provided to zinc-deficient populations. Zinc deficiency is widespread among children in developing countries and occurs in most part of Latin America, Africa, the Middle East, and South Asia. In a presentation to the Global Forum for Health Research in 1999, Dr. R.E. Black estimated that annual Disability Adjusted Life Years (DALYs) due to zinc deficiency were 57,425,209.

Zinc has been identified to play critical roles in metallo-enzymes, poly-ribosomes, the cell membrane, and cellular function, leading to the belief that it also plays a central role in cellular growth and in the function of the immune system. Although the theoretical basis for a potential role of zinc has been postulated for quite some time, actual convincing evidence of its importance in child health has come from recent randomized controlled trials on zinc supplementation.

In trials evaluating the therapeutic effect of zinc supplementation on acute diarrhoea from Indonesia, India (2 trials), and Bangladesh (2 trials) that have been recently subjected to a meta-analysis (1), zinc-supplemented children had a 16% faster recovery [95% confidence interval (CI) 6 to 22%]. With zinc supplementation, there was also a 20% reduction (95% CI -2 to 38%) in the odds of acute episodes lasting for over seven days. Furthermore, in three of the trials with appropriate outcome measures, reductions in diarrhoeal severity in zinc-supplemented children were observed when compared with control children. The analyses concluded that zinc supplementation given along with appropriate fluids and foods during acute diarrhoea reduces the duration of illness and its severity.

However, since publication of the trials incorporated in the above-mentioned pooled analysis, a number of additional studies evaluating the therapeutic effect of zinc supplementation on the clinical course of acute diarrhoea have been completed. A meeting was convened in New Delhi, India, on 7-8 May 2001 to review the research findings of all the studies that had investigated the effect of zinc supplementation on the clinical course of acute diarrhoea.
diarrhoea and to draw conclusions concerning its efficacy.

These additional studies have been divided in three groups: hospital-based studies, community-based studies, and studies in which zinc was mixed with oral rehydration solution (ORS).

**Hospital-based studies**

Four studies evaluating the efficacy of zinc supplementation on the clinical course of acute diarrhoea in hospitalized children, not included in the above-mentioned pooled analysis, were identified, and results of these studies were reviewed in the meeting. The characteristics of these studies are described in Table 1.

In these studies, children hospitalized with signs of dehydration due to acute watery diarrhoea were randomized to receive either zinc supplementation or placebo. Supplementation was administered by the study staff as long as the child was hospitalized, ensuring perfect adherence to treatment. In the two studies in which supplementation was done for a maximum of 14 days, administration of the supplement was under the responsibility of caretaker after discharge from hospital. The results presented below only concern data collected during hospitalization.

A recently-published study (2) conducted in Calcutta, India, to evaluate the efficacy of zinc supplementation (40 mg per day) on the clinical course of acute diarrhoea in 80 mild-to-moderately-malnourished children showed that children in the zinc-supplemented group had a significantly shorter duration of diarrhoea (70±10 vs 103±17 hours; p=0.0001) and passed less liquid stools per day while they still had diarrhoea (1.5±0.7 vs 2.4±0.7 kg; p=0.0001).

Another recently-completed hospital-based study conducted in New Delhi, India (S. Bhatnagar. Personal communication) was reviewed to compare the efficacy of zinc with placebo in a double-blind randomized clinical trial in children aged 3-36 months with acute diarrhoea of less than 72 hours duration. In this study, the major outcome variables were stool output, duration of diarrhoea, and need for unscheduled intravenous fluids. Two hundred eighty-seven children were admitted in the study—143 were randomized to receive zinc, while 144 were randomized to receive placebo. The results of this study showed that the duration of diarrhoea was significantly reduced in the group of children receiving zinc (effect size 0.77, 95% CI 0.59 to 0.99), the number of episodes lasting more than five days (6/132 vs 16/134; adjusted OR=0.35, 95% CI 0.13 to 0.96).

<table>
<thead>
<tr>
<th>Location</th>
<th>Age group (in months)</th>
<th>Sample size zinc/control</th>
<th>Nutrition criteria</th>
<th>Zinc salt</th>
<th>Dosage per day</th>
<th>Duration of supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>India (Calcutta)</td>
<td>3-24</td>
<td>44/36</td>
<td>WFA &lt;80%</td>
<td>Sulphate</td>
<td>40 mg</td>
<td>14 days</td>
</tr>
<tr>
<td>India (New Delhi)</td>
<td>3-36</td>
<td>143/144</td>
<td>WFH &gt;65%</td>
<td>Sulphate</td>
<td>15 or 30 mg*</td>
<td>14 days</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>1-6</td>
<td>182/93</td>
<td>WFA &gt;60%</td>
<td>Acetate</td>
<td>5 or 20 mg†</td>
<td>Period of illness</td>
</tr>
<tr>
<td>Brazil</td>
<td>3-60</td>
<td>37/37</td>
<td>None</td>
<td>Sulphate</td>
<td>22 or 45 mg‡</td>
<td>Maximum of 5 days</td>
</tr>
</tbody>
</table>

* 15 mg in children aged less than 12 months and 30 mg in children aged over 12 months
† Two treatment groups: one group received 5 mg of zinc daily, while the other group received 20 mg daily
‡ 22 mg in children aged less than 10 months and 45 mg in children aged 10 months and older
WFA=Weight-for-age; WFH=Weight-for-height

However, results of a study conducted in Bangladesh to evaluate the effect of two different doses of zinc acetate (5 mg and 20 mg per day) on the severity of acute watery diarrhoea in 275 breastfed infants aged less than six months did not show any effect of zinc supplementation in this age group on disease severity, defined as duration of diarrhoea and stool output or on progression to persistent diarrhoea (A. Brooks. Personal communication). It should be noted that, if there were no benefits associated with zinc supplementation in this age group, daily zinc supplementation (5 mg or 20 mg) was well-tolerated by these young infants; most of them were low-birth-weight infants.

Finally, results of a study conducted in Brazil to assess the efficacy of zinc in the treatment of 74 children with acute watery diarrhoea showed that the duration of diarrhoea was reduced by 52%, and the number of watery stools was reduced by 76% in the group of children receiving zinc (L.E. Cuevas. Personal communication).

**Community-based studies**

Four recently-completed and unpublished community-based studies, comparing the efficacy of zinc...
supplementation on the clinical course of acute diarrhoea with that of a placebo or a control, were identified and discussed during the meeting. The general characteristics of these studies are presented in Table 2.

Table 2. Characteristics of community-based studies

<table>
<thead>
<tr>
<th>Location</th>
<th>Age group (in months)</th>
<th>Sample size zinc/control</th>
<th>Nutrition criteria</th>
<th>Zinc salt</th>
<th>Dosage per day</th>
<th>Duration of supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal</td>
<td>6-35</td>
<td>897/452</td>
<td>None</td>
<td>Gluconate</td>
<td>15 or 30 mg</td>
<td>Until 7 days after recovery</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>3-59</td>
<td>5,866/6,015*</td>
<td>None</td>
<td>Acetate</td>
<td>20 mg</td>
<td>14 days</td>
</tr>
<tr>
<td>South India</td>
<td>3-35</td>
<td>545/547</td>
<td>No severe malnutrition</td>
<td>Sulphate</td>
<td>5 or 10 mg</td>
<td>Until 7 days after recovery</td>
</tr>
<tr>
<td>North India</td>
<td>3-35</td>
<td>404/401</td>
<td>None</td>
<td>Gluconate</td>
<td>15 or 30 mg</td>
<td>Until recovery</td>
</tr>
</tbody>
</table>

* Child/years

In the study conducted in Nepal (T. Strand. Personal communication), children were randomized into three groups: zinc, zinc and vitamin A, and placebo. Supplements were administered daily by a field worker visiting the household of the enrolled child. Results of this study showed that daily supplementation of zinc during acute diarrhoea reduced episode duration (relative hazard-time to recovery 0.79, 95% CI 0.68 to 0.93) and the risk of diarrhoea lasting more than seven days (RR 0.57, 95% CI 0.38 to 0.86). The study also showed that the administration of zinc caused excess vomiting (RR 1.9, 95% CI 1.5 to 2.3). However, there was no indication that this excess vomiting was interfering with oral rehydration therapy.

The study conducted in Bangladesh used a cluster randomized design. Children were enrolled in the study at the time they consulted Bari mothers or village health workers for diarrhoea (A. Baqui. Personal communication). Children in the zinc clusters were advised to take 20 mg elemental zinc daily for 14 days regardless of the duration of diarrhoea, and daily administration of zinc was under the responsibility of the caretaker. In control clusters, children were given the standard treatment without zinc. In both the areas, children received feeding advice, ORS, and other treatments. Efforts were made to maximize use of the study-recommended therapy, but no attempts were made to change care-seeking pattern. Bari mothers in the treatment clusters recorded the numbers of zinc bottles and ORS packets given to each patient. Results of this study showed that the duration of diarrhoea and hospitalization for diarrhoea were reduced by 23% in clusters where children received zinc. The prevalence of diarrhoea was significantly reduced (14%) as well as non-injury deaths (50%) in the zinc clusters. In addition, ORS-use rate increased by 20% and antibiotic-use rate decreased by 60% in the zinc clusters.

In the study conducted in South India, supplements were administered during diarrhoea and for seven days after recovery. However, contrary to other studies, results did not show any effect of zinc supplementation on the clinical course of diarrhoea (S. Sazawal. Personal communication).

In North India, children of an urban slum consulting for diarrhoea were randomized to receive, in addition to ORS, either zinc or a placebo until recovery from illness (R. Bahl. Personal communication). Results of this study showed that daily supplementation of zinc during acute diarrhoea significantly reduced the duration of the episode, the proportion of episodes lasting more than five days, and stool frequency. However, the study also showed that the administration of zinc caused excess vomiting.

Studies evaluating the efficacy of zinc-ORS

Two studies conducted in Cuba and North India evaluated the efficacy of zinc supplementation on the clinical course of acute diarrhoea when administered with ORS. The characteristics of these studies are described in Table 3.

In the study conducted in Cuba, ORS-zinc did not have any beneficial advantage over ORS solution given alone (L.E. Cuevas. Personal communication). However, in the study conducted in North India, ORS-zinc was superior to ORS alone but less efficacious in reducing the duration of the episode than zinc supplements given separately from ORS solution (R. Bahl. Personal communication).
Table 3. Characteristics of studies evaluating efficacy of zinc-ORS

<table>
<thead>
<tr>
<th>Location</th>
<th>Age group (in months)</th>
<th>Sample size zinc/control</th>
<th>Nutrition criteria</th>
<th>Zinc salt</th>
<th>Dosage per litre of ORS</th>
<th>Duration of supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuba</td>
<td>3-36</td>
<td>48/49</td>
<td>None</td>
<td>Sulphate</td>
<td>20 mg</td>
<td>Until recovery</td>
</tr>
<tr>
<td>North India</td>
<td>3-35</td>
<td>402/401</td>
<td>None</td>
<td>Gluconate</td>
<td>40 mg</td>
<td>Until recovery</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The discussions in the meeting considered the following questions:

1. Does zinc supplementation during treatment of acute diarrhoea have an effect on duration of the episode and stool volume/frequency, need for unscheduled IV therapy, and death?

Results of studies included in the pooled analysis mentioned above, together with the results of the additional studies presented at the meeting, were reviewed.

These studies showed a trend for the reduction in the proportion of episodes lasting more than seven days in children receiving zinc supplementation, and in one study, the reduction was statistically significant (Table 5).

Eight studies collected information on stool volume or frequency. In all the studies, zinc supplementation was associated with a reduction in stool output/frequency (Table 6).

It is clear that zinc supplementation has a clinically significant beneficial impact on the clinical course of acute diarrhoea, reducing the severity and duration of diarrhoea.

2. Is the effect of zinc supplementation on acute diarrhoea dependent on age or nutritional status?

Zinc deficiency often complicates severe malnutrition (8,9). However, review of all the above studies did not show any greater effect of zinc supplementation according to age (above 3 months of age) or nutritional status (less-nourished). In fact, a study conducted in

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**Table 4. Effect of zinc on duration of diarrhoea/time to recovery**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Ref. no.</th>
<th>No. of subjects zinc/placebo</th>
<th>Dose of zinc (elemental)</th>
<th>Difference in mean duration in days (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sachdev, 1988</td>
<td>3</td>
<td>25/25</td>
<td>40 mg</td>
<td>-0.4 (-1.4, 0.6)</td>
</tr>
<tr>
<td>Faruque, 1999</td>
<td>4</td>
<td>341/340</td>
<td>14.2 or 40 mg</td>
<td>-1.0 (-1.8, -0.2)</td>
</tr>
<tr>
<td>Dutta, 2000</td>
<td>2</td>
<td>44/36</td>
<td>40 mg</td>
<td>-1.4 (-1.6, -1.1)</td>
</tr>
<tr>
<td>Cuevas, 2001 (unpublished)</td>
<td></td>
<td>37/37</td>
<td>22.5 mg (3-9 months)</td>
<td>-1.3 (-1.9, -0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45 mg (10-60 months)</td>
<td></td>
</tr>
<tr>
<td>Sazawal, 2001 (unpublished)</td>
<td></td>
<td>547/547</td>
<td>5 mg (&lt;12 months)</td>
<td>0.1 (-0.2, 0.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mg (&gt;12 months)</td>
<td></td>
</tr>
<tr>
<td>Hidayat, 1998</td>
<td>5</td>
<td>739/659</td>
<td>4.5 mg/kg</td>
<td>0.92 (0.83, 1.02)</td>
</tr>
<tr>
<td>Sazawal, 1995</td>
<td>6</td>
<td>456/481</td>
<td>20 mg</td>
<td>0.79 (0.69, 0.90)</td>
</tr>
<tr>
<td>Roy, 1997</td>
<td>7</td>
<td>57/54</td>
<td>20 mg</td>
<td>0.85 (0.57, 1.28)</td>
</tr>
<tr>
<td>Bhatnagar, 2001 (unpublished)</td>
<td></td>
<td>132/134</td>
<td>15 mg (&lt;12 months)</td>
<td>0.77 (0.59, 0.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 mg (&gt;12 months)</td>
<td></td>
</tr>
<tr>
<td>Bahl, 2001 (unpublished)</td>
<td></td>
<td>404/401</td>
<td>15 mg (&lt;12 months)</td>
<td>0.89 (0.80.0.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 mg (&gt;12 months)</td>
<td></td>
</tr>
<tr>
<td>Strand, 2001 (unpublished)</td>
<td></td>
<td>442/449</td>
<td>15 mg (&lt;12 months)</td>
<td>0.79 (0.68, 0.93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 mg (&gt;12 months)</td>
<td></td>
</tr>
<tr>
<td>Baqui, 2001 (unpublished)</td>
<td></td>
<td>620/632</td>
<td>20 mg</td>
<td>0.77 (0.69, 0.86)</td>
</tr>
</tbody>
</table>

CI = Confidence interval

With regard to the time from enrollment in the study to recovery from diarrhoea, it is clear, as shown in Table 4, that zinc supplementation has a significant beneficial effect on the clinical course of acute diarrhoea. In 11 of 12 studies, zinc supplementation was associated with a reduction in the duration of the episode, and in 8, the reduction was statistically significant.

Five studies recorded data on the proportion of episodes lasting more than seven days. Results of all acute diarrhoea, reducing the severity and duration of diarrhoea.

2. Is the effect of zinc supplementation on acute diarrhoea dependent on age or nutritional status?

Zinc deficiency often complicates severe malnutrition (8,9). However, review of all the above studies did not show any greater effect of zinc supplementation according to age (above 3 months of age) or nutritional status (less-nourished). In fact, a study conducted in...
Delhi found no relationship (Table 7) between mean plasma zinc levels or proportion of children with plasma zinc levels below 60 mg/dL and anthropometric values (R. Bahl. Personal communication).

These confirm the results of the pooled analysis (1), which found similar benefits of zinc supplementation in subgroups divided by age and nutritional status.

Concerning age, the limited data collected on children aged less than six months, especially on children aged less than three months, do not allow any conclusion with regard to the effect of zinc supplementation in this age group. However, evidence to date indicates that it is safe to give zinc supplements in this age group.

![Table 5. Effect of zinc on proportion of episodes lasting more than seven days](image)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Ref. no.</th>
<th>No. of subjects</th>
<th>Dose of zinc (elemental)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hidayat, 1998</td>
<td>5</td>
<td>739/659</td>
<td>4.5 mg/kg</td>
<td>0.72 (0.48, 1.07)</td>
</tr>
<tr>
<td>Sazawal, 1995</td>
<td>6</td>
<td>456/481</td>
<td>20 mg</td>
<td>0.85 (0.60, 1.19)</td>
</tr>
<tr>
<td>Roy, 1997</td>
<td>7</td>
<td>57/54</td>
<td>20 mg</td>
<td>0.77 (0.33, 1.79)</td>
</tr>
<tr>
<td>Bahl, 2001</td>
<td>(unpublished)</td>
<td>404/401</td>
<td>15 mg (&lt;12 months)</td>
<td>0.61 (0.33, 1.12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 mg (&gt;12 months)</td>
<td></td>
</tr>
<tr>
<td>Strand, 2001</td>
<td>(unpublished)</td>
<td>442/449</td>
<td>15 mg (&lt;12 months)</td>
<td>0.57 (0.38, 0.86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 mg (&gt;12 months)</td>
<td></td>
</tr>
</tbody>
</table>

CI=Confidence interval

3. Is there evidence that zinc supplementation is efficacious globally (in developing countries), or that it varies according to settings with different dietary patterns, rates of diarrhoea, mortality rates, etc.?

Although most of the studies on this topic were conducted in South East Asia, the available data do not allow to suspect that the beneficial effect of zinc supplementation may be different from region to region. In fact, the study conducted in South America, albeit small, showed similar treatment effect as those seen in studies conducted in the Indian sub-continent (L.E. Cuevas. Personal communication).

Although dietary patterns vary between the different populations studied, all studies have been undertaken in populations with evidence of zinc deficiency, and where low intake of foods of animal origin with high bioavailable zinc is common.

4. Is there an impact of zinc supplementation on vomiting?

Data on vomiting following the administration of zinc were reviewed. Only the study from Nepal reported any significant increase in vomiting among children receiving zinc compared to those who received placebo. In this study, children were given a dose of zinc equivalent to three times the recommended daily allowance (RDA) (15-30 mg per day) as zinc gluconate. However, other studies giving similar amounts of zinc gluconate did not report any increase in vomiting among children randomized to the zinc treatment groups.

From these data, it is difficult to determine if the increased vomiting was due to the relatively high dose administered or to the zinc formulation that did not mask the taste efficiently. Further research to determine the most acceptable zinc formulation is required.

5. Is there an impact of zinc supplementation when given together with other micronutrients?

A double-blind, randomized controlled trial in children aged 6-35 months was conducted in India to determine the efficacy of a combination of micronutrients, including zinc, vitamin A, folic acid, vitamin B12, vitamin D, selenium, and manganese, in children with acute diarrhea compared to zinc alone (R. Bahl. Personal communication and 10). In the zinc group, children aged over 12 months received 30 mg, and infants received 15 mg elemental zinc daily, while children in the multiple micronutrients group received 1-3 RDA(s) of zinc, vitamin A, folic acid, vitamin D, selenium, and manganese. Household visits were made twice a week till recovery from diarrhoea.

The risk of continuation of diarrhoea was reduced in zinc [relative hazards (RH) 0.86, 0.76 to 0.97] and multiple micronutrient (RH 0.84, 0.75, 0.95) groups compared to the control group. In both zinc and multiple micronutrient groups, the total number of watery stools was also lower [incidence rate ratio (IRR) 0.69, 95% CI 0.59 to 0.81 and 0.70, 0.60 to 0.82 respectively]. The beneficial effect of multiple micronutrients was...
somewhat greater than that of zinc on the proportion of children with diarrhoea lasting over seven days (OR 0.32, 0.15 to 0.69 for multiple micronutrients compared to controls; OR 0.58, 0.31 to 1.10 for zinc compared to controls).

This study showed that zinc alone was just as efficacious as multiple micronutrients, including zinc, in reducing the severity of acute diarrhoea.

6. What is the ideal daily dose and form of zinc?

Should it be given in single daily dose or in split doses for the management of diarrhoea?

Three types of zinc salts were used in the studies mentioned above: zinc sulphate, zinc acetate, and zinc gluconate. It does not appear from the review that the type of zinc salt used in the studies had an impact on the results.

Similarly, the studies reviewed do not allow to assess precisely the ‘ideal’ dose of zinc to administer daily, since all studies gave zinc doses comprising 1-4 RDA(s). It can, however, be said very confidently that a daily dose of 20 mg of zinc is efficacious in reducing the severity and duration of diarrhoea episode. In hospitalized children, this amount of zinc can be given as 2-3 divided doses daily, while in the community, one single dose of 20 mg per day is safe and efficacious.

7. Is it feasible to add zinc to ORS and would it have the same efficacy?

Results of two studies that have evaluated the efficacy of zinc when added to ORS have clearly shown that this strategy is feasible. No after-taste, no increased vomiting, and no difference in consumption of ORS were observed with the ORS-zinc mixture. However, results of the two studies are less clear in terms of efficacy. In one small study conducted in Cuba, ORS-zinc was equivalent to ORS alone, while in the other conducted in India, ORS-zinc was superior to ORS alone but less efficacious in reducing the duration of the episode than were zinc supplements given separately from ORS.

These results can be explained by the fact that the amounts of zinc consumed through ORS-zinc are markedly less than the amounts of zinc consumed when zinc supplements are given separately from ORS. Indeed, the average amount of ORS consumed during an episode of diarrhoea is about 44 mL/kg per child per day for a maximum of two days (11). Therefore, with the concentrations of zinc contained in ORS tested in the two studies (Cuba 20 mg/L and India 40 mg/L), the

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Ref. no.</th>
<th>No. of subjects</th>
<th>Dose of zinc (elemental)</th>
<th>Effect on stool frequency</th>
<th>Incidence rate ratio (95% CI)</th>
<th>Geometric mean ratio (95% CI)</th>
<th>Difference in means or medians (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sachdev, 1988</td>
<td>3</td>
<td>25/25</td>
<td>40 mg</td>
<td>-1.7 (-4.1, 0.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sazawal, 1995</td>
<td>6</td>
<td>456/481</td>
<td>20 mg</td>
<td>-2.0 (-3.6, -0.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuevas, 2001</td>
<td>(unpublished)</td>
<td>37/37</td>
<td>22.5 mg (3-9 months)</td>
<td>-5.9 (-9.5, -2.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45 mg (10-60 months)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bahl, 2001</td>
<td>(unpublished)</td>
<td>404/401</td>
<td>15 mg (&lt;12 months)</td>
<td>0.73 (0.63, 0.84)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 mg (&gt;12 months)</td>
<td>0.91 (0.85, 0.97)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strand, 2001</td>
<td>(unpublished)</td>
<td>442/449</td>
<td>15 mg (&lt;12 months)</td>
<td>0.73 (0.52, 1.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 mg (&gt;12 months)</td>
<td>0.73 (0.52, 1.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhatnagar, 2001</td>
<td>(unpublished)</td>
<td>132/134</td>
<td>15 mg (&lt;12 months)</td>
<td>0.73 (0.52, 1.02)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>30 mg (&gt;12 months)</td>
<td>0.73 (0.52, 1.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutta, 2000</td>
<td>2</td>
<td>44/36</td>
<td>40 mg</td>
<td>-900 g (-1200, -590)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roy, 1997</td>
<td>7</td>
<td>57/54</td>
<td>20 mg</td>
<td>-91 g</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Daily stool frequency
† Total stool number
CI=Confidence interval
average consumption of zinc was 8 mg per day for two
days in Cuba and 16 mg per day for two days in India.
These quantities are well below the quantities of zinc
consumed when the supplements are given separately
from ORS (20 mg per day for 7-14 days).

To increase the intake of zinc, one option would be
to increase the concentration of zinc contained in ORS.
However, because ORS can be consumed in large
quantities (up to 3-4 L per day), it is important to
determine the maximum concentration of zinc that can
be added to ORS without compromising safety.

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Table 7. Plasma zinc status and anthropometry:
baseline data from the Delhi zinc-ORS study
in children with acute diarrhoea

<table>
<thead>
<tr>
<th>Anthropometry</th>
<th>Mean (SD) plasma zinc</th>
<th>Plasma zinc &lt;60 µg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Stunted</td>
<td>66.7 (13.1)</td>
<td>153 29.8</td>
</tr>
<tr>
<td>(n=514) (&lt;-2 HAZ)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-stunted</td>
<td>65.1 (14.1)</td>
<td>190 37.8</td>
</tr>
<tr>
<td>(n=503) (&gt;-2 HAZ)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wasted</td>
<td>66.5 (15.6)</td>
<td>109 35.2</td>
</tr>
<tr>
<td>(n=310) (&lt;-2 WHZ)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-wasted</td>
<td>66.7 (12.7)</td>
<td>234 33.1</td>
</tr>
<tr>
<td>(n=707) (&gt;-2 WHZ)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HAZ=Height-for-age z-score
WHZ=Weight-for-age z-score

CONCLUSIONS AND RECOMMENDATIONS

- Zinc supplementation, given at a dose of about 2
  RDAs per day (10-20 mg per day) for 14 days, is
efficacious in reducing the severity of diarrhoea and
the duration of the episode significantly.

- There is now enough evidence demonstrating the
efficacy of zinc supplementation on the clinical
course of acute diarrhoea. However, effectiveness
studies to assess different strategies for delivering
zinc supplementation to children with diarrhoea
should be undertaken. These studies should
investigate the feasibility, sustainability, and cost-
effectiveness of different zinc-delivery mechanisms,
and monitor variables, such as consumption of ORS,
antibiotic-use rate, non-diarrhoea morbidity, and
overall mortality.

- Further research is required to determine the effect
of zinc supplementation in infants aged less than six
months.

- Although the type of zinc salt does not seem to
influence efficacy, it is important to determine the
best formulation of zinc to minimize the side-effects
of zinc administration, essentially vomiting.

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