Preventing Zinc Deficiency in Early Infancy: Impact on Morbidity, Growth and Mortality

Sunil Sazawal and Pooja Malik

Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Md., USA

Introduction

The importance of zinc as a nutrient essential for growth, tissue repair, neural and cognitive development, development and functionality of the immune system has been known for a long time [1]. A zinc deficiency in depletion experiments produces hepatosplenomegaly, hypogonadism, dermatitis, alopecia, mental disturbances, growth retardation, infections, and eventually death. Worst hit of all is the immune system resulting in decreased T and B cells, suppressed delayed hypersensitivity, cytotoxic activity and antibody production [2], thereby making an individual more vulnerable to infections [3].

Due to the abundance of zinc in the environment, in many of the foods, and the lack of a good biomarker of deficiency, the occurrence of deficiency was considered unlikely until Prasad et al. [4] first documented it in 1961. A low zinc status at birth, losses due to frequent diarrhea, increased zinc demands for catch-up growth, inadequate weaning practices and dependency on plant-based diets which reduce the bioavailability of whatever zinc is present in diet, are some of the factors that may predispose infants and children to mild to moderate zinc deficiency [5]. Again until a decade back the focus was always on a clinical deficiency of nutrients and its signs and symptoms. Over the past decade there has been substantial progress in the understanding the role of subclinical forms of micronutrient deficiencies in the causation of morbidity and mortality.
Zinc in Breast-Fed Infants at Birth and during 6 Months of Lactation

During the first few months after birth, newborns depend on milk for their zinc intake. Breast milk zinc has a greater bioavailability than zinc in formula [6, 7], the difference being attributed to a citrate-rich fraction, the presence of lactoferrin, and the lower casein or phosphorous content of breast milk [8–13]. Yet regardless of the type of feeding, serum zinc levels experience a drop during the first 2 months after birth. The assumption of the adequacy of zinc in breast milk for neonates is based on a lack of symptoms and normal plasma zinc levels. Low birth weight infants may, however, develop zinc deficiency [9, 10], and the absence of symptoms in most infants has been attributed to zinc being released from remodeling bone, thereby delaying the onset of any symptomatic zinc deficiency until the 2nd year of life [9].

Theoretical Considerations for Zinc Inadequacy in Breast Milk

Assuming a milk production of 700 ± 175 ml at 1 month [11] and 750 ± 120 ml/day at 3 months [11] or an average of 850 ml [12] in the first 6 months and the National Research Council’s recommended dietary allowance for zinc of 3 mg/day for 0–6 months [13], breast milk should have at least 3.5 μg/ml of zinc to provide one recommended dietary allowance. Among low socioeconomic Amazonian women, Lethi [14] found 95, 97 and 100% of women in months 1, 2 and 3 of lactation to be below 3.5 μg/ml. In an Indian population Rajlakshmi and Srikantia [15] found a zinc concentration of 4.56 ± 0.35 μg/ml in colostrum, which fell to 2.54 ± 0.3, 1.89 ± 0.3 and 1.24 ± 0.2 μg/ml during months 1, 2 and 3, respectively. There were significantly lower breast milk zinc levels in lower socioeconomic mothers as compared to well-to-do mothers. The poor nutritional status of the mother in these settings may also lead to lower breast milk volume, thus possibly requiring an even higher concentration of zinc. According to the calculations of zinc requirements with the levels of zinc in breast milk at 6 months, about 80–100% zinc would have to be absorbed, merely to allow for soft tissue accretion. These calculations do not take into account the deposition of zinc in the bone [16]. Complementary foods, such as cereals often given to young infants, may be high in phytates which reduce the bioavailability of zinc by interfacing with absorption [17, 18].

Transient Symptomatic Zinc Deficiency

Moynahan and Barnes [19, 20] first noted the association of zinc deficiency with *Acrodermatitis enteropathica*. In premature infants, transient
symptomatic zinc deficiency (TSZD) has been reported in breast-fed infants
[21–29] and Husnoo et al. [30] described 1 premature breast-fed infant with
low zinc levels. These children had serum zinc levels below normal at the time
of diagnosis, they responded rapidly to zinc supplementation, and the zinc
supplement could be discontinued without recurrence of symptoms. Of the
7 studies measuring breast milk zinc levels in mothers, 6 [21–28] had low
while 1 had normal levels [29]. TSZD is thought to be due to negative zinc
balance and high demand for rapid growth in preterm infants, supporting the
concept that zinc deficiency of some degree may be occurring in infants fed
breast milk alone.

Zinc Supplementation

**Effects on Morbidity, Growth and Mortality**

A number of controlled trials have been undertaken to investigate the role
of preventing zinc deficiency in early infancy and childhood in last 7 years.
These studies have provided new understanding of the occurrence of zinc
deficiency and the impact of its prevention on morbidity, growth and mortality.
There have been 2 pooled/meta-analyses published on the effects of zinc
supplementation on morbidity and 1 meta-analysis published on the effects on
growth which was recently updated. In the present review we have expanded
the meta-analysis for morbidity impact to include all the studies that have been
reported after this was published, and also include all available information
from recent studies reporting mortality impact. Both meta-analyses and this
review have been restricted to published and unpublished randomized
controlled trials of oral zinc supplementation. This review includes a total of
12 studies reporting the therapeutic effect of zinc supplementation, 11 trials
evaluating the effect of zinc supplementation on the prevention of diarrhea, 5
trials reporting effects on pneumonia, 3 reporting effects on malaria morbidity,
3 reporting effects on mortality, and 4 evaluating the effects of a short course
of supplementation on the subsequent prevention of diarrhea and pneumonia.
Growth effects are based on meta-analyses of 37 trials reported recently. As
many trials have not presented data in the first 6 months or 1 year separately
we have tried to present the overall effect and review comparisons of effect in
infants vis-à-vis older children based on available data.

**Effects on Diarrhea**

Diarrhea is still the major cause of childhood mortality estimated to cause
more than 3 million deaths in children [31]. Two measures of the effects of
zinc supplementation on diarrhea morbidity are described in the literature
and presented in this review. First the ‘therapeutic effect’ which describes the
effect of giving zinc supplementation to a child during an episode of diarrhea
on the outcome of that episode. Second the ‘preventive effect’ which
describes the effect of zinc supplementation given over a prolonged period on the occurrence and severity of diarrhea morbidity.

**Therapeutic Effects of Zinc Supplementation on Diarrhea**

The role of zinc in acute and persistent diarrhea has been evaluated in 19 randomized controlled trials. Of these, 15 were on acute diarrhea and 4 were on persistent diarrhea. The characteristics of the trials are summarized in table 1.

In the pooled analysis of acute diarrhea [32] that used data from 3 trials (table 2), zinc-supplemented children had a 15% lower probability of continuing diarrhea on a given day (95% CI 8, 22%) than did the children in the control group. In the effect size analysis, which used data from 5 acute diarrhea trials (table 2), a summary estimate of the effect size for a reduction of diarrhea was 16% (95% CI 7, 26%). There was a 15–27% reduction in episodes lasting more than 7 days, and studies which had data on stool frequency or stool weight demonstrated a reduction in these severity indicators as well (table 2).

Studies that were completed after the publication of the pooled analysis were recently reviewed [33]. Study characteristics of these studies are also presented in table 1. There essentially were 3 types of studies: hospital-based studies that supplemented hospitalized children; community based studies, and studies in which zinc was mixed with an oral rehydration solution (ORS). All studies except 1 found that zinc supplementation has a significant beneficial effect on the clinical course of acute diarrhea including duration, stool frequency and episodes lasting more than 7 days.

In 5 studies that evaluated the effect of zinc supplementation on persistent diarrhea (table 1), zinc-supplemented children had a 24% lower probability of continuation of diarrhea on a given day (95% CI 8, 38%) than did control children (table 2) and an effect size of 29% (95% CI 6–52%). There was also a significant effect on adverse outcome defined as treatment failure or death.

Most of the studies enrolled children after 3 months of age and there is not sufficient data to analyze specific estimates in children in first 6 months of life. However, the pooled analysis by age group, both for acute and persistent diarrhea, indicated a similar effect in 3- to 11- and more than 11-month-old children. The summary estimate for <12-month-old children for acute diarrhea was 1.14 (1.01–1.29) and that for persistent diarrhea was 1.40 (1.08–1.83). These results clearly indicate that zinc supplementation provides clinically significant benefit to infants and children recovering from acute or persistent diarrhea. Zinc can thus become an important component of diarrheal disease treatment programs in developing countries. This has recently been acknowledged in the recommendation of a WHO consultative group as well [33].

**Prevention of Diarrhea Morbidity**

The preventive effect of zinc supplementation on acute diarrhea data from 15 randomized controlled trials reported to date has been evaluated. Of these
Table 1. Study characteristics of the trials evaluating the therapeutic effect

<table>
<thead>
<tr>
<th>Location [ref]</th>
<th>Age group months</th>
<th>Zinc group, n</th>
<th>Control group, n</th>
<th>Zinc salt</th>
<th>Dosage</th>
<th>Duration of supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials included in pooled analysis for acute diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indonesia [42]</td>
<td>3–35</td>
<td>739</td>
<td>659</td>
<td>Acetate</td>
<td>4–5 mg/kg</td>
<td>Until recovery</td>
</tr>
<tr>
<td>India [43]</td>
<td>6–35</td>
<td>456</td>
<td>481</td>
<td>Gluconate</td>
<td>20 mg</td>
<td>Until recovery</td>
</tr>
<tr>
<td>Bangladesh [44]</td>
<td>3–24</td>
<td>57</td>
<td>54</td>
<td>Acetate</td>
<td>20 mg</td>
<td>Until recovery</td>
</tr>
</tbody>
</table>

Recent trials not included in the pooled analysis

<table>
<thead>
<tr>
<th>Location</th>
<th>Age group months</th>
<th>Zinc group, n</th>
<th>Control group, n</th>
<th>Zinc salt</th>
<th>Dosage</th>
<th>Duration of supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital-based studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India, New Delhi [45]</td>
<td>3–36</td>
<td>143</td>
<td>144</td>
<td>Sulfate</td>
<td>15 or 30 mg</td>
<td>14 days</td>
</tr>
<tr>
<td>Bangladesh [46]</td>
<td>1–6</td>
<td>182</td>
<td>93</td>
<td>Acetate</td>
<td>5 or 20 mg</td>
<td>Period of illness</td>
</tr>
<tr>
<td>Brazil [47]</td>
<td>3–60</td>
<td>37</td>
<td>37</td>
<td>Sulfate</td>
<td>22 or 45 mg</td>
<td>Maximum of 5 days</td>
</tr>
</tbody>
</table>

Community-based studies

<table>
<thead>
<tr>
<th>Location</th>
<th>Age group months</th>
<th>Zinc group, n</th>
<th>Control group, n</th>
<th>Zinc salt</th>
<th>Dosage</th>
<th>Duration of supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal [48]</td>
<td>6–35</td>
<td>897</td>
<td>452</td>
<td>Gluconate</td>
<td>15 or 30 mg</td>
<td>Until recovery</td>
</tr>
<tr>
<td>Bangladesh [49]</td>
<td>3–59</td>
<td>5,866</td>
<td>6,015</td>
<td>Acetate</td>
<td>20 mg</td>
<td>Until 7 days after recovery</td>
</tr>
<tr>
<td>South India [50]</td>
<td>3–35</td>
<td>547</td>
<td>547</td>
<td>Sulfate</td>
<td>5 or 10 mg</td>
<td>14 days</td>
</tr>
<tr>
<td>North India [51]</td>
<td>3–35</td>
<td>404</td>
<td>401</td>
<td>Gluconate</td>
<td>15 or 30 mg</td>
<td>Until 7 days after recovery</td>
</tr>
</tbody>
</table>

Zinc added to oral rehydration solution

<table>
<thead>
<tr>
<th>Location</th>
<th>Age group months</th>
<th>Zinc group, n</th>
<th>Control group, n</th>
<th>Zinc salt</th>
<th>Dosage</th>
<th>Duration of supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuba [52]</td>
<td>3–36</td>
<td>48</td>
<td>49</td>
<td>Sulfate</td>
<td>20 mg</td>
<td>Until recovery</td>
</tr>
<tr>
<td>North India [53]</td>
<td>3–35</td>
<td>402</td>
<td>401</td>
<td>Gluconate</td>
<td>40 mg</td>
<td>Until recovery</td>
</tr>
</tbody>
</table>

Trials included in pooled analysis for persistent diarrhea

<table>
<thead>
<tr>
<th>Location</th>
<th>Age group months</th>
<th>Zinc group, n</th>
<th>Control group, n</th>
<th>Zinc salt</th>
<th>Dosage</th>
<th>Duration of supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peru [54]</td>
<td>6–35</td>
<td>139</td>
<td>136</td>
<td>Gluconate</td>
<td>20 mg</td>
<td>Until recovery</td>
</tr>
<tr>
<td>Bangladesh [55]</td>
<td>3–24</td>
<td>95</td>
<td>95</td>
<td>Acetate</td>
<td>20 mg</td>
<td>Until recovery</td>
</tr>
<tr>
<td>Bangladesh [56]</td>
<td>6–24</td>
<td>44</td>
<td>44</td>
<td>Acetate</td>
<td>20 mg</td>
<td>Until recovery</td>
</tr>
<tr>
<td>Pakistan [57]</td>
<td>6–36</td>
<td>43</td>
<td>44</td>
<td>Sulfate</td>
<td>3 mg/kg</td>
<td>Until recovery</td>
</tr>
</tbody>
</table>

1 Personal communications [37].
11 were ‘long supplementation’ (table 3) in which the supplements were provided for the entire period of morbidity surveillance and 4 trials (table 3) were ‘short-supplementation trials’ in which the supplements were given for a short period (2 weeks), and the morbidity surveillance was done for a subsequent period of 4–12 weeks. The characteristics of these trials are presented in table 3. Individual trial results for the preventive effects on zinc deficiency in early infancy are shown in table 2.
### Table 3. Study characteristics of the trials evaluating the effect of zinc supplementation on the prevention of diarrhea

<table>
<thead>
<tr>
<th>Trials [Ref.]</th>
<th>Total child-years</th>
<th>Enrollment age months</th>
<th>Zinc supplement</th>
<th>Control</th>
<th>Supplement duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>zinc group</td>
<td>control group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India [53, 54]</td>
<td>122.9</td>
<td>124.8</td>
<td>6–35</td>
<td>10 mg as gluconate</td>
<td>Both groups vit. A, B, D, E</td>
</tr>
<tr>
<td>Mexico [55]</td>
<td>116</td>
<td>117.1</td>
<td>18–36</td>
<td>20 mg as methionate (half with iron)</td>
<td>Placebo (half with iron)</td>
</tr>
<tr>
<td>Papua New Guinea [56]</td>
<td>75.3</td>
<td>80.7</td>
<td>6–60</td>
<td>10 mg as gluconate</td>
<td>Placebo</td>
</tr>
<tr>
<td>Peru [57]</td>
<td>36.1</td>
<td>37.4</td>
<td>6–35</td>
<td>10 mg as gluconate</td>
<td>Placebo</td>
</tr>
<tr>
<td>Vietnam [58]</td>
<td>30.8</td>
<td>30.8</td>
<td>4–36</td>
<td>10 mg as sulfate</td>
<td>Placebo</td>
</tr>
<tr>
<td>Guatemala [59]</td>
<td>23.2</td>
<td>22.9</td>
<td>6–9</td>
<td>10 mg as sulfate</td>
<td>Placebo</td>
</tr>
<tr>
<td>Jamaica [60]</td>
<td>7.1</td>
<td>6.2</td>
<td>6–24</td>
<td>5 mg as sulfate</td>
<td>Both groups vit. A, B, C, D</td>
</tr>
<tr>
<td>Burkina Faso [37]</td>
<td>134.39</td>
<td>134.21</td>
<td>6–31</td>
<td>12.5 mg as sulfate</td>
<td>Placebo</td>
</tr>
<tr>
<td>Ethiopia(^a)</td>
<td>46</td>
<td>46</td>
<td>6–12</td>
<td>10 mg as sulfate</td>
<td>Placebo</td>
</tr>
<tr>
<td>India(^a)</td>
<td>361.7</td>
<td>368.2</td>
<td>6–30</td>
<td>10 mg (young), 20 mg (old) as gluconate</td>
<td>Placebo</td>
</tr>
<tr>
<td>Bangladesh(^a)</td>
<td>48.8</td>
<td>21.9</td>
<td>12–35</td>
<td>20 mg as gluconate</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

**Short course supplementation trials**

<table>
<thead>
<tr>
<th>Trials [Ref.]</th>
<th>Total child-years</th>
<th>Enrollment age months</th>
<th>Zinc supplement</th>
<th>Control</th>
<th>Supplement duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh [61]</td>
<td>12.8</td>
<td>13.5</td>
<td>3–24</td>
<td>20 mg as acetate</td>
<td>Both groups vit. A, B, D, E</td>
</tr>
<tr>
<td>Pakistan [62]</td>
<td>10.8</td>
<td>10.6</td>
<td>6–36</td>
<td>20 mg as sulfate</td>
<td>Both groups vit. A, B, C, D</td>
</tr>
<tr>
<td>Bangladesh [63]</td>
<td>0.6</td>
<td>0.7</td>
<td>3–24</td>
<td>20 mg as acetate</td>
<td>Both groups vit. A, B, D, E</td>
</tr>
</tbody>
</table>

\(^a\) Unpublished studies.
Zinc Deficiency in Early Infancy

diarrhea incidence, prevalence and persistent diarrhea incidence along with pooled analysis estimates using random effects model are presented in table 4. The most interesting part of the analysis is the consistency of impact across the studies. Pooled analysis indicates a 19% reduction in the incidence of diarrhea and 26% reduction in days the child was sick with diarrheal symptoms in ‘long-supplementation’ studies. The estimates were similar for short-supplementation studies though there was more variability between studies. Pooled analysis of 7 studies where data on the incidence of persistent diarrhea were available yielded a significant 31% reduction in the incidence of persistent diarrhea.

Most of these studies enrolled children after 6 months of age and estimates below that age are not available, but analysis of data by age group comparing effects in children below 1 year with older children seems to suggest that similar effects can be expected in younger children. Analysis of data for diarrhea morbidity in the studies among children below 12 months is presented in table 5. Although the sample size in most studies was not adequate to perform a subgroup analysis, overall estimates of 9 and 13% reduction in the incidence of diarrhea, and 22 and 38% reduction in the prevalence in long-supplementation trials and short-supplementation trials, respectively, were indicative of a similar impact in younger age as well.

Prevention of Pneumonia

Of the 11 long-supplementation trials, the effect of zinc supplementation on pneumonia morbidity has been reported in 5 studies. These data have been included in the updated meta-analysis for this review (table 4). All studies reported a reduction in pneumonia (table 4), the impact estimate ranging from 17 to 68%. A meta-analysis of these data indicates an overall impact of 34% (95% CI 27–47%). Again there were no data in the <6 months age group and analysis of data comparing impact in children <12 months in fact demonstrated a higher impact than in older children. This is consistent with the fact that in infants, pneumonia is a higher contributor to severe morbidity and mortality. The pooled estimate showed a reduction in pneumonia of 42% (95% CI 3–65%) for 4 studies that reported data in children <12 months.

Malarial Morbidity

Although there are data from animal studies indicative of a potential benefit of zinc supplementation in malaria [34], data from human studies are limited and results more variable. So far, 3 trials have been reported which evaluated the effect on malarial morbidity of zinc supplementation. In the Gambia, using a twice-weekly 70-mg zinc supplementation, Bates et al. [35] reported a 32% reduction (p = 0.09) in clinic visits due to malaria. In Papua New Guinea using daily 10-mg zinc supplementation, Shankar et al. [36] reported a reduction of 38% (95% CI 5–60%; p = 0.037) in health center-based episodes of Plasmodium falciparum. Using a 12.5-mg daily zinc
Table 4. Effect of preventive zinc supplementation on the incidence of persistent diarrhea, dysentery and pneumonia

<table>
<thead>
<tr>
<th>Location [ref]</th>
<th>Effect on diarrheal episode, days</th>
<th>Persistent diarrhea</th>
<th>Dysentry</th>
<th>Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long supplementation trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India [53, 54]</td>
<td>0.92 (0.84–1.00)</td>
<td>0.94 (0.90–0.98)</td>
<td>0.79 (0.57, 1.09)</td>
<td>0.57 (0.34, 0.93)</td>
</tr>
<tr>
<td>Guatemala [59]</td>
<td>0.82 (0.71–0.93)</td>
<td>0.75 (0.69–0.81)</td>
<td>0.25 (0.08, 0.68)</td>
<td></td>
</tr>
<tr>
<td>Vietnam [58]</td>
<td>0.56 (0.40–0.78)</td>
<td>0.45 (0.37–0.54)</td>
<td>0.44 (0.10, 1.54)</td>
<td>0.56 (0.39, 0.80)</td>
</tr>
<tr>
<td>Peru [57]</td>
<td>0.88 (0.79–0.99)</td>
<td>0.85 (0.79–0.91)</td>
<td>1.24 (0.38, 4.15)</td>
<td>0.83 (0.35, 1.95)</td>
</tr>
<tr>
<td>Mexico [55]</td>
<td>0.63 (0.47–0.83)</td>
<td>0.70 (0.60–0.81)</td>
<td>0.77 (0.16, 3.30)</td>
<td></td>
</tr>
<tr>
<td>Burkina Faso [37]</td>
<td>0.84 (0.72–0.97)</td>
<td>0.87 (0.79–0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jamaica [60]</td>
<td>0.92 (0.58–1.44)</td>
<td>0.80 (0.63–1.01)</td>
<td></td>
<td>0.32 (0.01, 6.21)</td>
</tr>
<tr>
<td>Papua New Guinea [56]</td>
<td>0.88 (0.63–1.22)</td>
<td>0.80 (0.76–0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.45 (0.29–0.72)</td>
<td>0.52 (0.40–0.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.83 (0.75–0.92)</td>
<td>0.80 (0.76–0.84)</td>
<td>0.76 (0.48, 1.22)</td>
<td></td>
</tr>
<tr>
<td>India&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.88 (0.83–0.93)</td>
<td></td>
<td></td>
<td>0.76 (0.58, 1.00)</td>
</tr>
<tr>
<td>Pooled estimate HLM</td>
<td>0.81 (0.72–0.90)</td>
<td>0.74 (0.64–0.86)</td>
<td>0.69 (0.48, 0.97)</td>
<td>0.66 (0.53, 0.83)</td>
</tr>
<tr>
<td><strong>Short supplementation trials</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh [61]</td>
<td>0.70 (0.47–1.06)</td>
<td>0.64 (0.52–0.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pakistan [62]</td>
<td>1.10 (0.57–2.12)</td>
<td>0.54 (0.38–0.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh [63]</td>
<td>1.11 (0.58–2.11)</td>
<td>0.77 (0.51–1.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.83 (0.75–0.93)</td>
<td>0.80 (0.76–0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled estimate HLM</td>
<td>0.84 (0.75–0.93)</td>
<td>0.71 (0.57–0.88)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Unpublished studies.
supplementation in Burkina Faso, Muller et al. [37] found no effect in the incidence of \textit{P. falciparum} malaria, relative risk 0.98 (95% CI 0.86–1.11). There is need for more data investigating the effect of zinc supplementation on malaria morbidity. A large ongoing supplementation trial in Pemba Zanzibar may provide more definitive information by September 2004.

\textbf{Effects on Growth: Meta-Analysis of Available Data}

Zinc-responsive growth stunting has been identified in many studies from several regions worldwide. Brown et al. [38] recently updated their previous meta-analyses to assess the effect of zinc supplementation on the growth. Of the original search of 447 articles, 37 met the inclusion criteria for the meta-analysis, published between 1976 and 2001. Of these, 34 data sets that were used for the analyses provided information for a total of 2,945 children with the mean ages ranging from newborn to 10 years.

The meta-analysis showed a significant positive effect on linear growth. Of the 33 data sets, 25 (75.8%) of the studies were positive with 10 showing a significant effect, in 8 (24.8%) the effect size was negative or 0. The overall effect size was 0.35 (95% CI 0.19–0.51; p < 0.001; fig. 2) confirming the role of zinc supplementation in linear growth. In the subgroup analyses the effect of zinc supplementation was 2-fold greater in studies in which the children were initially stunted (\( \leq 2 \) initial height-for-age \( Z \) scores), 0.46 (95% CI 0.17, 0.75) than in normal children (\( \geq 2 \) initial height-for-age \( Z \) scores). There was no detectable effect of zinc supplementation on children's weight-for-height index, possibly indicating that zinc is more likely to influence linear growth. Also in these analyses there was in fact a trend towards a higher impact in

\begin{table}[h]
\centering
\begin{tabular}{llll}
\hline
\textbf{Location [ref]} & \textbf{Diarrheal episode} & \textbf{Diarrheal days} & \textbf{Pneumonia episodes} \\
\hline
\textit{Long supplementation trials} & & & \\
India [53, 54] & 1.05 (0.91–1.20) & 1.09 (1.02–1.17) & 0.70 (0.34–1.40) \\
Guatemala [59] & 0.82 (0.71–0.93) & 0.75 (0.69–0.81) & \\
Vietnam [58] & 0.40 (0.91–0.81) & 0.41 (0.29–0.60) & 0.47 (0.17–1.17) \\
Peru [57] & 0.95 (0.75–1.19) & 0.89 (0.77–1.03) & 0.37 (0.09–1.18) \\
Jamaica [60] & 0.87 (0.42–1.82) & 0.61 (0.43–0.86) & 0.16 (0.00–4.75) \\
Papua New Guinea [56] & 1.37 (0.68–2.89) & 1.09 (0.64–1.87) & \\
Pooled random effects & 0.91 (0.75–1.09) & 0.78 (0.61–1.01) & 0.58 (0.35–0.97) \\
\hline
\textit{Short supplementation trials} & & & \\
Bangladesh [61] & 0.76 (0.50–1.17) & 0.67 (0.54–0.83) & \\
Pakistan [62] & 0.98 (0.40–2.50) & 0.52 (0.33–0.80) & 0.89 (0.24–3.43) \\
Bangladesh [63] & 1.00 (0.45–2.23) & 0.64 (0.37–1.10) & 0.92 (0.40–2.07) \\
Pooled random effects & 0.87 (0.55–1.38) & 0.62 (0.47–0.82) & 0.94 (0.43–2.04) \\
\hline
\end{tabular}
\caption{Effect of preventive zinc supplementation on diarrhea and pneumonia at ages < 12 months: long and short supplementation trials}
\end{table}
younger children <1 year as compared to children 1–4 years or >4 years suggesting that these findings would be relevant to infancy (fig. 3).

**Effect of Zinc on Mortality**

Given the effects of zinc supplementation on diarrhea and pneumonia morbidity, which are the main causes of mortality in preschool children, this is a strong case for the impact of zinc supplementation on mortality. To date there have been 3 small studies which reported the mortality effects of zinc supplementation. These studies have also provided the best confirmation to date of the potential role of zinc supplementation in early infancy. The data on mortality impact are summarized in table 6. In a randomized double-blind controlled trial with a daily supplementation of 5 mg zinc from 1 to 9 months of age in full-term small-for-gestational age infants, Sazawal et al. [39] reported a 68% reduction in mortality in the zinc group compared to the control group. The survival analysis of the data (fig. 1) clearly indicates that impact extends right from 1 month after supplementation and is not restricted to beyond 6 months of age. Lira et al. [40] from Brazil also reported a smaller zinc supplementation trial in full-term low birth weight infants supplemented for the first 8 weeks of life. Due to problems with the study supplement, this study ended up being analyzed in two parts. Part one was a concurrent control group

![Fig. 1. Impact of zinc supplementation on mortality in small-for-gestational-age infants [64].](image-url)
Zinc Deficiency in Early Infancy

Table 6. Effect of zinc supplementation on mortality

<table>
<thead>
<tr>
<th>Location [ref]</th>
<th>Age range</th>
<th>Zinc n</th>
<th>No Zinc n</th>
<th>Effect on mortality</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>India [64]</td>
<td>SGA infants(^1)</td>
<td>581</td>
<td>573</td>
<td>0.32 (0.12, 0.89)</td>
<td>p = 0.028</td>
</tr>
<tr>
<td>Brazil [65] 1 mg</td>
<td>LBW infants(^2)</td>
<td>68</td>
<td>66</td>
<td>0.50 (0.13, 2.01)</td>
<td>p = 0.334</td>
</tr>
<tr>
<td>Concurrent control</td>
<td>Before, after</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh [66]</td>
<td>3–59 months(^3)</td>
<td>5,866</td>
<td>6,015</td>
<td>0.49 (0.25, 0.94)</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

\(^1\) SGAs were full-term supplemented 1–9 months.
\(^2\) LBWs were also full-term supplemented for 8 weeks.
\(^3\) In the Bangladesh study 2,070 child-years were contributed by the age group 3–11 months.
\(^4\) Child-years of follow-up.

![Fig. 2](image_url) Zinc supplementation and growth effect: impact on height [38].

comparison of a placebo with a 1-mg zinc supplement group, and part two was a non-concurrent control group comparison of a placebo group with a 5-mg zinc supplement group. Although there may be concerns about study design, due to which these data were not included in meta-analysis, it is presented here as it provides some data in the <6-month age group and helps to confirm the
potential role of zinc in young infants. The study found a 50% reduction in mortality in both comparisons; these were however statistically not significant due to the small sample size. This study also found a significant reduction in diarrhea morbidity for diarrhea defined by mothers (OR 0.72; 95% CI 0.52–0.99) and for diarrhea defined by liquid or semi-liquid stools (≥3/day; OR 0.52; 95% CI 0.38–0.72). Baqui et al. [41] recently reported a cluster randomized comparison study from Bangladesh in which 8,070 children contributed 11,881 child-years of observation. In control clusters every diarrheal episode was treated with zinc, 20 mg for 2 weeks, in addition to ORS and compared to areas where only ORS was given. There was a significant reduction in non-injury deaths in the zinc group rate ratio 0.49 (95% CI 0.25–0.94). Although the study obviously did not have sample size to analyze data by age group, out of total of 11,881 child-years of follow-up 671 were 3–5 months old and 1,399 were 6–11 months of age. Given the considerably higher mortality in the 1st year this impact would not be likely if there was no effect in children under 1 year. Three large studies, one in Zanzibar, the second in Nepal and the third in India, are underway. They are evaluating the impact of zinc supplementation on mortality. The data from these studies in the next 2 years will provide more detailed and precise estimates of the effects on mortality.

Conclusion

Our understanding of the importance of preventing zinc deficiency in infants and children as regards its impact on infectious disease and mortality is rapidly
increasing. The recent studies, especially the randomized controlled trials summarized in this report, have on one hand shown the widespread occurrence of zinc deficiency in infants and preschool children and on the other hand have confirmed the impact of preventing zinc deficiency on morbidity and mortality. Although not separately analyzed, the data regarding its role in the second 6 months of life are fairly strong and compelling to warrant action, be it in terms of supplementation programs or fortification strategies. With regard to the data for the first 6 months of life, however, the need for more information is clear. Recent studies documenting the mortality impact in small-for-gestational-age children and suggestions of impact in a low birth weight study from Brazil clearly indicate it may be just as important in the first 6 months as has been documented in latter part of preschool age. In terms of interventions to prevent zinc deficiency, strategies in the first 6 months of life would have to be different than those in older children and would need to be tested independently.

References

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Discussion

**Dr. El Hodhod:** In Egypt we added zinc to oral rehydration solutions 3–4 years ago and its impact on the duration and severity of the diarrheal episodes is very evident. Another point, what about the assessment of zinc status in such mothers and infants? Serum zinc alone is not an accurate method to assess zinc status and there are no standards for hair, nails and so on. What can we do? The diurnal variation of zinc in breast milk has been reported. Does this variation do something to the lactating infants? In one study it was demonstrated to be high in the morning and low in the evening, and most of the women now are working and they don’t breast-feed their infants in the morning.

**Dr. Sazawal:** Let me answer the first question first. The indicator of zinc status has been debated, and a problem is that these studies were not done for a long time period, and the debate probably continues. But I can give you my view on that, taken from the data that I didn’t present because of time limitations, the zinc data from all these studies. My understanding of this area at the moment is that plasma zinc is not a very good indicator if you are looking at an individual prediction of zinc deficiency, but it is a very good indicator if you are looking at the group description of deficiency, and probably the best indicator that we have at present in addition to dietary intake. The problem in dietary intake: we are doing dietary intake studies at the moment in India, and it is a nightmare because in a lot of these parts of the world there are no food tables which actually give the phytate, and zinc intake cannot be evaluated from the diet by simply doing traditional dietary 24-hour recalls because bioavailable zinc comes through. But other than that I think plasma zinc is a fairly good indicator for a group comparison. In these studies the thinking has been shown that clear-cut effects are demonstrated. In our study, the supplemented group increased from a mean of 60 to a mean of 80 and the control group was exactly 60 both before and after. There were also concerns, and again I didn’t present those data here, about what happens in illness because we know that in illness or in the acute phase reaction interleukin-1 is related to a zinc shift which goes into the liver. The estimations of zinc deficiency can sometimes be artificially inflated, but the fraction of that in the totality, and in these studies we are talking about approximately 37–40% of children with <60 mg/dl, and the fraction that that particular factor contributes is very small. So I feel that plasma zinc is a fairly good indicator for looking at a population, but if you are treating a child in a clinical setting I would not recommend it. Now your second question about lactation, I guess the question that you are asking is the lack of effect.
**Dr. El Hodhod:** It was the diurnal variation of zinc.

**Dr. Sazawal:** There is not only a lot of diurnal variation in the same woman, there is also a variation between women, and that was one of the things that we noted in our study. These data were from a supplementation trial that we did in lactation, and even in developing countries a big variation in breast milk zinc was found. But the data that I showed were collected in a standardized fashion so they would be all collected in the same time periods, the standardized interval from the last feed, and the standardized interval from the last breast-feeding done. Yet the interesting part is that it is exactly the same as what has been reported in the US. However, a point earlier about these concepts about vitamin A: what a lot of us have ignored is the quantity of breast milk. I feel that is the key and we don’t have a handle on it, and the concentrations might be preserved but that is about it. We don’t know whether the quantities of breast milk are preserved or not and that would make a big difference.

**Dr. Al Frayh:** The protection effect of zinc in diarrhea, I did not understand it very well, but I understood from your presentation that zinc has a protective effect in diarrhea. Are you saying that it protects from post-diarrheal symptoms or it protects from the ongoing diarrhea? Did the zinc deficiency result from diarrhea? You say that it protects from diarrhea. Or does it protect from the ongoing diarrhea as a post-diarrheal symptom?

**Dr. Sazawal:** I showed two kinds of data. One of the questions that we were trying to address was the issue of a therapeutic effect of zinc. The question that was asked is, if you see a child with diarrhea in addition to Oral Rehydration Solution, you give zinc supplementation, what is going to be the outcome of that episode? The therapeutic trials that I showed investigated the effect of supplementation started during diarrhea on the outcome of that episode, and the data show that there is an about 20% reduction in the duration of that episode. There is an about 20–30% reduction in the episodes that last more than 7 days. What I didn’t show here is that there is an about 30–35% reduction in treatment failures and mortality in persistent diarrhea. So one effect is a therapeutic effect of zinc given during diarrhea, which is fairly quick. In our study the analysis shows that the effect kicks in at about the third supplementation. Now the second complement, the earlier data I showed, essentially on the preventive effect of zinc supplementation, address the question whether zinc deficiency potentially places a child at high risk of getting diarrhea or at high risk of getting longer episodes of diarrhea if he/she is zinc deficient. So if we supplement a child, what we are potentially doing is preventing deficiency, and by preventing deficiency we are able to see a reduction in incidence which, translated into biomedical terms, is essential. In these communities all of us are exposed to pathogens, but not all of us get sick. These are randomized control trials in the same population, some children are getting zinc, some are not getting zinc, then exposure is similar. Given a similar exposure if your zinc status is adequate you have less likelihood of getting disease.

**Dr. Barclay:** In your review on the effects of zinc supplementation on growth you showed that there were 20 or 25 studies and the overall effect on growth was small. In one of these studies [1] we saw an about 1-cm increase in growth over a 15-month period, but looking at the dietary data we also realized that these children are only consuming about 60% of their energy requirements that are the same as their protein requirements. So in fact I was surprised that without any substrate to work on these children show an increase in growth. Do you think these other studies also suffer from the same thing, that in zinc-deficient populations there may be limited energy intake?

**Dr. Sazawal:** I can give you two comments on that question. When I designed the small-for-gestational age trial, the reason why I put in calcium, phosphorus, etc. into the factorial design, was that at that point in time I was biased toward there being other elements which limit growth and that is why a bigger effect of growth may be
seen from zinc for example than we see because of that. All kinds of studies have been reviewed: studies which start with children who were stunted to identify higher deficiency; studies in populations where there is not much malnutrition. What the review does show is that there is a higher impact if the subjects were malnourished. But to answer your second question, is it the limitation of caloric intake or intake of other micronutrients for example that has limiting effect on growth? Personally I would say no, because I have at least 3 data sets from my own studies. Two data sets were started when I was at the medical institute: children were physically randomized and given food which had calories, food which had proteins, and food which had micronutrients. The meals were delivered at home and we ensured that the child ate it, and there was no impact. I do have a feeling that growth is something which is not that straightforward as a limiting factor. I cannot say if we, for example, give zinc or iron in the first trimester of pregnancy or earlier that it may have an effect on growth. My feeling is that you look at the data, look at data set after data set after data set, look at growth at 1 year and see what is the predictor. In all the studies, I have seen that the strongest single predictor that stands up is birth weight. Your nutrient intake in the 1st year doesn't stand up, your supplementation of vitamin A doesn't stand up, supplementation of zinc doesn't stand up, nothing even comes close, the moment you put birth weight into the model everything else is eliminated. So my feeling, at least of the literature that is available today, is that we don't have evidence that this is the case.

Dr. Pettifor: There are some theoretical concerns about the use of zinc supplementation in HIV-positive infants. Are there any data to suggest that it is harmful?

Dr. Sazawal: The first thing I said was that we don't actually have data to say either. The problem with HIV is that there are data which suggest both, and all the data that are there are basically observational data. There are animal models and in vitro studies in which zinc was added to the media and the replication is decreased. There are data showing that the multiplication or immune response is better if zinc is given, as is expected. On the other hand there have been some association studies where again people are relating the taking of a supplement with time to disease, and some increased risk was found. So I feel that at the moment we don't know. Theoretically there should not be, unless there are some mechanisms that we are not aware of by which zinc-increased levels are going to improve the replication of virus, which seems unlikely to me. But there are at least two ongoing studies, supplementation trials in high HIV populations, and in the near future we should have an answer to that.

Dr. Young: I would like to come back to our Saudi colleague's question. You asked a number of questions. First, would zinc supplementation minimize the incidence of diarrheal episodes? Second, what was the mechanistic hypothesis that provided the rationale for your asking the question in the first place?

Dr. Sazawal: The problem with zinc is that you are never short of mechanical hypotheses. Let me give some examples, but I could give more. There have been studies, at least two, that have shown that the permeability of the membrane improves. We know that zinc has a membrane-stabilizing effect. We know that it will help in cell regeneration, so theoretically you could improve enterocyte regeneration and healing, and that was one of the reasons why there was a belief in some of the things that I have discussed with the gastroenterologists who are saying why don't you analyze viral diarrheas versus other diarrheas because potentially it could have more effect on Rota Virus diarrheas because Rota Virus causes more mucosal damage than does for example ETEC. So there is a set of mechanisms that could be operational at the local gastrointestinal level. So that is one set of mechanisms. The second set of mechanisms is related to the immune response, which is related to clearance of the pathogen. Studies in Animal Models have shown that in zinc deficiency state, there are more chances of developing Pneumonia after an exposure. There are a lot of mechanisms at the local gut level, there are
mechanisms which are more centralized which will be through the immune response, signifying multi-pronged actions of zinc. On discussion with Australian Colleague who is working on ciliary movements of various mucosas, and he told me that the ciliary movement increases in zinc rich media. So there are lots of small mechanisms but if you ask me which one I can’t say.

Dr. West: In the factorial trials done today were there any that included iron and if so, is there any evidence of antagonism between zinc and iron on any of the outcomes examined so far?

Dr. Sazawal: The only study with iron that had a factorial design was by Rosaldo et al. [2], and there the iron group had no effect but there was no adverse kind of effect evident. This study had a very small sample size. There are two other studies by Penny et al. [3], one in Peru, which was not a factorial study but had zinc, placebo and everything, and the everything group did worse than the placebo group in everything, including diarrhea. We haven’t still figured out why, but one of the hypotheses given is that due to high concentration of Ascorbic acid in the supplement which caused bad taste and thus was not very palatable for children. So there was ascorbic acid and iron, and my assumption is that could be one kind of place but there isn’t any clear-cut evidence in a randomized control trial. Even in terms of morbidity impact if iron, most of the studies, the studies are from either malaria areas or developed world, there is very little evidence from the developing country settings in that context. So it would be interesting to look at it in these studies.

Dr. Zlotkin: Just to carry on with this question. The Dietary Reference Intake Committee has set a relatively low level for zinc in the Canadian and American context, and the critical adverse effect they identified was the effect of zinc intake on copper status. The doses that you listed in your slides were anywhere between 1 and 40 mg of zinc in some studies. Is there any evidence that you may be impacting copper status by giving a fairly hefty dose of zinc?

Dr. Sazawal: This issue comes up whenever we discuss these data, and in fact I was going to ask that question when Dr. Allen was presenting the data in the morning because I don’t know. I can tell you what the data are but what is not clear to me, and I haven’t got a clear answer from anybody in the copper field, is what is an indicator of copper deficiency and what happens to that indicator in the first 1 year, in the first 2 years of life?

Dr. Zlotkin: The committee used erythrocytic superoxide dismutase (ESOD) as an indicator.

Dr. Sazawal: I know that the committee used ESOD and I know Dr. Calkin has a strong bias on that but the only data set that I know of that showed some effect on plasma copper was in a study by Bhutta et al. [4] in which it was given in hospitalized severely malnourished children who obviously would have reason to have copper deficiency, and he showed a decrease in the plasma copper but when he used ESOD there was no change. I will back off a bit and give you the data are. The data, at least from other studies that we have done, using 20 mg of zinc given for 6 months to these children and we did not give copper, that is essential because the supplements did not have copper and we did a phospholipid plasma copper assessment, there was no effect on plasma copper assessment levels. The study in Pakistan showed a minimal decrease in the plasma copper levels. There is another data set which is going to be published, from Delhi, which gave between 3 and 4 recommended daily allowances (RDAs) of zinc, and the problem in that study is that actually if you see the copper levels in Delhi they are, according to the international or Western norms, abnormal on the higher side, so you have fairly high copper levels to begin with but there is some evidence of a decrease in copper levels. Now what does that mean? But in our study we try to go one step further and do hematological investigations as well and we absolutely could not demonstrate any effect. In the kind of
studies that we are doing we reviewed those data and it was clear that up to 2 RDAs beyond 6 months of age there are enough data to say there isn’t a problem with copper, but even when you are going to higher doses, for example >100mg of zinc which has been used for membrane stabilizing effect in sickle cells patients, all you need to do is add a trace amount of copper into the supplement. But there aren’t data in the first 6 months of life and that is what we are collecting.

References