



World Health Organization

Workshop to Review the Results of Studies Evaluating the Impact of Zinc Supplementation on Childhood Mortality and Severe Morbidity

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Conclusions and Next Steps

1. Overall conclusions

- 1.1 From the two large studies on mortality conducted in Nepal and in Pemba ^{1,2} it appears that daily zinc supplementation in children less than 3 years of age leads to a modest non-significant 7-8% reduction in mortality. All infants and children enrolled in these two studies received six monthly high dose Vitamin A capsules. When all of the prevention trials examining the impact on mortality of zinc supplementation in young children (excluding trials that only included selected specific groups such as low birth weight or malnourished children) are viewed together, the mortality reduction was a statistically significant 9%.
- 1.2 In view of the results of all the trials examining the impact of zinc supplementation on mortality, morbidity and growth, a consensus was reached on the need to develop new feasible approaches to improve the intake of zinc and its bio-availability in young children, in order to achieve adequate population coverage.
- 1.3 One such approach is the provision of zinc as part of the routine management of diarrhoea, and potentially of other infectious diseases. Evidence based measures and/or operational research to support the effective implementation of routine treatment of all diarrhoea episodes with ORS and zinc are necessary.

2. Impact of preventive zinc supplementation on mortality in young children

- 2.1 Seven studies with information on the impact of zinc supplementation, given alone, on mortality outcomes were identified. However, these studies are heterogeneous in terms of study populations:

- four studies measured the impact of zinc supplementation on unselected population of young children (Burkina-Faso, Bangladesh, Nepal and Pemba) ¹⁻⁴;
- two studies measured the impact of zinc supplementation on selected populations of young children (two studies were conducted on Low Birth Weight (LBW)/Small for Gestational Age (SGA) infants (Brazil, India)) ^{5,6};
- one study enrolled ill children with diarrhoea, with subsequent home based zinc supplementation for 14 days (Bangladesh) ⁷.

Sites	Population	Zinc salt	Dose	
Burkina-Faso ³	Unselected	All children aged 6-31 months	Zinc sulfate (tablets) (Biolectra Zinc, Munich)	12.5 mg/day
Bangladesh ⁴		All children aged 2-12 months	Zinc acetate (syrup) (ACME Lab. Dhaka)	70 mg once a week
Nepal ²		All children aged 1-35 months	Zinc sulfate (tablets) (Nutriset, France)	10 mg/day
Pemba ¹		All children aged 1-48 months	Zinc sulfate (tablets) (Nutriset, France)	10 mg/day
Brazil ⁶	Selected	LBW infants recruited at 1 month and followed until 6 months old	Zinc sulfate (syrup)	5 mg/day
India ⁵		SGA infants recruited at 1 month and followed until 9 months old	Zinc sulfate (syrup)	5 mg/day
Bangladesh ⁷		Children with diarrhoea aged 3-59 months	Zinc acetate (syrup) (ACME Lab., Dhaka)	20 mg/day

2.2. The 4 studies that have enrolled unselected populations ¹⁻⁴, show protective point estimates for reducing mortality following zinc supplementation ranging from 0.15 to 0.93. The pooled reduction is 9% (95% CI 0% to 18%; p=0.05).

In the 2 studies for which data per age group is available (Nepal and Pemba) ¹⁻², there appears to be a differential effect by age, with larger effect size in older children (>12 months): a 18 to 20% reduction in mortality in children above 12 months of age (statistically significant in Pemba), although there was a 4-6% non-significant increase in mortality among younger children.

Age group	Pemba study ¹	Nepal study ²
0-12 months	1.06 (0.87 - 1.29)	1.04 (0.83 - 1.41)
>12 months	0.82 (0.68 - 1.00)	0.80 (0.60 - 1.06)

At this stage, the overall pooled estimate is largely determined by the two very large trials (Nepal and Pemba), which may be different from the others studies in a number of characteristics, e.g., nature of the supplement, morbidity pattern (e.g. malaria), provision of Vitamin A supplements, etc. Also, it should be noted that the impact of daily zinc supplementation on plasma zinc in these 2 trials was less than in earlier preventive zinc supplementation trials.

- 2.3 The studies conducted among selected populations, LBW and SGA infants (Brazil, India)⁵⁻⁶, show a pooled RR for reducing mortality of 0.35 (CI 95%, 0.16-0.78).
- 2.4 In the studies conducted in children with diarrhoea⁷, the rate of non-injury deaths in the group of children receiving zinc in addition to ORS as part of diarrhoea management was considerably lower than in the group of children that was just receiving ORS (RR 0.49, 95% CI 0.25 to 0.94).

3 Impact of preventive zinc supplementation on morbidity in young children

- 3.1 A review of a large number of studies (n=11) that were primarily designed to evaluate the impact of preventive zinc supplementation (5 to 20 mg/day) on morbidity in young children (<5 yrs) showed a consistent reduction in the incidence of diarrhoea and Acute Lower Respiratory Infections (ALRI)⁸. This review, however, included studies having enrolled children from selected as well as unselected populations. Since publication of this review an additional 7 studies on the same topic have been completed, showing overall a similar impact of zinc supplementation^{3-4, 9-13}.

In all these trials, which were conducted in different regions of the world, the effects on diarrhoea incidence were found to be large and statistically significant for older children (>12 months). In infants below 12 months of age, zinc supplementation was associated with a modest non-significant reduction in diarrhoea incidence. Further analysis of these studies is required to determine the impact of age on ALRI incidence.

- 3.2 In the two large mortality trials conducted in Nepal and in Pemba, impact on diarrhoea and ALRI was assessed as follows:
 - Nepal: weekly household visits on four stratified random samples of 1200 children, enrolled one year apart;
 - Pemba: passive surveillance of all hospitalizations.

In both studies, there was no significant impact on diarrhoea and ALRI morbidity following zinc supplementation, which is inconsistent with the results of earlier studies on zinc supplementation and morbidity. The analysis did not identify severe ALRI and severe diarrhoea, on which greater effect has been previously reported. Therefore, the totality of data on the impact of zinc supplementation on morbidity in selected and unselected populations should be reviewed, paying special attention to

issues of dose, formulation, definitions of morbidity outcomes and other modifying factors.

In these 2 trials, it should be noted that the impact of daily zinc supplementation on plasma zinc was less than in earlier preventive zinc supplementation trials.

4 Impact of zinc supplementation as part of treatment of diarrhoea

4.1 Studies evaluating the impact of zinc supplementation on the management of diarrhoea (5 to 45 mg/day) can be placed into two categories:

(i) studies assessing the impact of zinc supplementation on the clinical outcome of the treated episode¹⁴; and

(ii) studies assessing the impact of zinc supplementation given during a diarrhoeal episode and for a few days following the end of the episode (14 days)¹⁵⁻¹⁶. The purpose of this approach was to influence the treated episode and also to prevent future morbidity – mortality over the ensuing 2 to 3 months.

4.2 The first set of studies showed that zinc supplementation given during an episode of diarrhoea is efficacious in improving the outcome of the treated diarrhoeal episode:

- reduction of diarrhoea duration and of the proportion of episodes lasting more than 7 days;
- reduction in the frequency and/or volume of stools.

Data from the second category of studies show that continuing supplementation for a few days after the end of the episode provides additional benefits, including decline in diarrhoeal incidence, and reduction in non-injury deaths (Bangladesh)⁷. In addition, the two large effectiveness studies conducted in Bangladesh and in India^{7,17}, have shown that when zinc and ORS are promoted together for the treatment of diarrhoea, as part of a diarrhoea control programme, important additional benefits were observed:

- increased ORS prescription rate;
- increased ORS use rates;
- decreased irrational antibiotic use rates;
- decrease antidiarrhoeals use rates; and
- reduction in hospitalization rates.

4.3 Results from 2 additional ongoing large effectiveness studies, conducted in Mali and Pakistan, will be available within the next 6 months which should further inform on this.

5 Impact of zinc supplementation on growth

5.1 A meta-analysis of studies evaluating the impact of zinc supplementation on growth has shown that zinc supplementation has a significant positive effect on linear

growth and weight gain in stunted and/or underweight populations, including among studies that enrolled children with a mean initial age of <12 months¹⁸.

Additional data on growth will be available from the studies conducted in Nepal and in Pemba.

6 Zinc and Iron interactions

6.1 Mortality

Three preventive zinc supplementation trials (India, Nepal and Pemba)^{1-2, 19} compared the effect on mortality of zinc plus iron/folic acid with that of iron/folic acid. None of these trials found an impact of zinc plus iron/folic acid on mortality, when compared to iron/folic acid alone, including in the sub-group of older children (>12 months), where a significant impact of zinc alone was demonstrated.

6.2 Morbidity

No consistent differences in morbidity between children receiving zinc alone versus those receiving zinc plus iron/folic acid was observed in the above-mentioned three large trials.

6.3 Biochemical indicators

Based on review of all published data, when iron and zinc are concurrently provided in the supplement, although their impact on biochemical indicators is still positive when compared to placebo, we observe a slightly diminished response on biochemical indicators:

- 12 trials assessed zinc in addition to iron for iron outcomes:
 - (i) 6 studies found no difference between iron alone or zinc in addition to iron;
 - (ii) 5 studies found small additional benefit of iron alone compared to zinc and iron (larger increase in Hb and/or serum ferritin); and
 - (iii) 1 study found greater benefit of joint supplementation (weekly) on ferritin.
- 7 trials assessed iron in addition to zinc for zinc outcomes (plasma zinc concentration or morbidity):
 - (i) 4 studies found no effect;
 - (ii) 2 studies found less effect on serum zinc with zinc and iron than zinc alone; and
 - (iii) 1 study found zinc and iron reduced diarrhea and ALRI morbidity more than zinc alone.

7. Next steps

7.1 Mortality

(i) Retrieve data sets from all available studies, including recently published morbidity trials, to look at effects by sex and month of age;

(ii) Sort out the supplement effect by serum zinc concentration, consumption of supplement prior to blood drawing, bio-availability of the supplement, and six monthly compliance related to impact.

7.2 **Morbidity**

(i) Examine the impact of modifying factors such as breastfeeding, dietary practices and other nutrient deficiencies, morbidity patterns (e.g. malaria), gender, age, change in plasma zinc, on the impact of zinc supplementation on morbidity;

(ii) Update the published pooled analysis in selected and unselected populations with recently published results.

7.3 **Growth**

Re-do meta-analysis on growth with a pooled data set to examine possible effects of modifying factors (e.g., gender, age, change in plasma zinc, etc.).

7.4 **Zinc plasma levels**

- **Bio-availability of zinc supplements**

Compare the bio-availability of different dosages of the zinc supplement used in the large mortality studies with that of zinc syrup, in children from the two sites (Nepal and Pemba).

- **Environmental [tropical] enteropathy**

Environmental Enteropathy (EE) has been shown to be very frequent in rural population of Aborigine infants with severe impairment of zinc absorption. If EE is endemic in later infancy in Nepal and Pemba, it could explain:

(i) the absence of any increase in plasma zinc with zinc supplementation in these two studies; and

(ii) the lack of benefit of zinc supplementation between 6-12 months, a period during which the young child is likely to have the most severe inadequacy in zinc intake from the diet. Therefore, we would like to propose:

- To undertake pilot gut function studies on infants aged 6-12 months in these two populations;
- If these studies give evidence of impaired gut function, to undertake zinc absorption studies using zinc stable isotope extrinsic label.

7.5 **Future studies** should evaluate how to safely deliver iron and to avoid interference between iron and zinc.

8. **Timeline and Responsibilities**

8.1 **Mortality**

(i) Retrieve data sets from all available studies, including recently published morbidity trials, to look at effects by sex and month of age.

(ii) Sort out the supplement effect by serum zinc concentration, consumption of supplement prior to blood drawing, bio-availability of the supplement, and six monthly compliance related to impact.

8.2 **Morbidity**

(i) Examine the impact of modifying factors such as breastfeeding, dietary practices and other nutrient deficiencies, morbidity patterns (e.g. malaria), gender, age, change in plasma zinc, on the impact of zinc supplementation on morbidity.

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- To undertake pilot gut function studies on infants aged 6-12 months in these two populations;
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8.5 **Future studies** should evaluate how to safely deliver iron and zinc to avoid interference between iron and zinc.

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