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Zinc Supplementation in Public Health

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Key Messages

- **Zinc supplementation as adjunct therapy in diarrhea shortens the duration of the illness.**
- **Preventive zinc supplements can reduce morbidity and mortality in young children.**
- **Zinc deficiency should be addressed in the context of other health and nutrition programs designed to ensure that all children meet their essential nutrient needs.**

Key Words

Zinc supplements · Diarrhea · Pneumonia · Child morbidity · Child mortality

Abstract

Zinc is necessary for physiological processes including defense against infections. Zinc deficiency is responsible for 4% of global child morbidity and mortality. Zinc supplements given for 10–14 days together with low-osmolarity oral rehydration solution (Lo-ORS) are recommended for the treatment of childhood diarrhea. In children aged ≥6 months, daily zinc supplements reduce the duration of acute diarrhea episodes by 12 h and persistent diarrhea by 17 h. Zinc supplements could reduce diarrhea mortality in children aged 12–59 months by an estimated 23%; they are very safe but are associated with an increase in vomiting especially with the first dose. Heterogeneity between the results of trials is not understood but may be related to dose and the etiology of the diarrhea infection. Integration of zinc and Lo-ORS into national programs is underway but slowly, procurement problems are being overcome and the greatest challenge is changing health provider and caregiver attitudes to diarrhea management. Fewer trials have been conducted of zinc adjunct therapy in severe respiratory tract infections and there is as yet insufficient evidence to recommend addition of zinc to antibiotic therapy. Daily zinc supplements for all children >12 months of age in zinc deficient populations are estimated to reduce diarrhea incidence by 11–23%. The greatest impact is in reducing multiple episodes of diarrhea. The effect on duration of diarrheal episodes is less clear, but there may be up to 9% reduction. Zinc is also efficacious in reducing dysentery and persistent diarrhea. Zinc supplements may also prevent pneumonia by about 19%, but heterogeneity across studies has not yet been explained. When analyses are restricted to better quality studies using CHERG (Child Health Epidemiology Reference Group) methodology, zinc supplements are estimated to reduce diarrheal deaths by 13% and pneumonia deaths by 20%. National-level programs to combat childhood zinc deficiency should be accelerated.

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Introduction

Zinc is essential for maintaining the structure and form of protein molecules; it is in many cases fundamental to their function as enzymes or structural proteins. Diverse physiological processes including cell replication are impacted by zinc deficiency. Of particular relevance to public health, zinc is necessary for immune defense systems, growth, intestinal function, and brain development [1].

It is estimated that 35% of child deaths can be attributed to undernutrition which increases the risk and severity of infectious diseases such as diarrheal disease, pneumonia and malaria [2]. Zinc deficiency is a common component of undernutrition and is associated with stunting and high rates of lower respiratory infections and diarrhea, particularly in children <5 years of age. It is estimated that, globally, zinc deficiency is responsible for 176,000 diarrhea-related and 406,000 pneumonia-related deaths of children <5 years of age and an estimated 4% of the global morbidity and mortality burden of young children [3–5].

This review will focus on zinc supplements and their role in child morbidity and mortality. Zinc supplementation has been used in two ways to combat zinc deficiency in young children: as an adjunct to treatment of common infectious diseases, especially diarrhea (table 1), and as a preventative supplement to reduce child morbidity and mortality. These strategies will be discussed in this paper.

Zinc as Adjunct Therapy in the Treatment of Diarrheal Disease

In 1988, Sachdev et al. [6] reported on a trial of zinc supplementation in children admitted to hospital with acute diarrhea in India. The zinc supplement reduced fecal output in children who were stunted or had low plasma concentrations of zinc. Further clinical trials in the community and in different parts of the world confirmed a beneficial effect of zinc supplements in diarrheal episodes and a combined analysis of the raw data concluded that zinc supplements resulted in a 15 and 24% lower probability of continuing diarrhea on a given day in acute episodes and persistent diarrhea (≥14 days), respectively [7]. The results of this analysis and additional reviews [8] of the role of zinc in the treatment of diarrhea led the WHO and UNICEF to issue a joint statement in 2004 updating the recommendations for the treatment of diarrhea to include the use of low-osmolarity oral rehydration solution (Lo-ORS), continued feeding and oral zinc supplements (fig. 1) [9]. This recommendation still stands.

WHO/UNICEF joint statement:
clinical management of acute diarrhea

Mothers and other caregivers should
- Prevent dehydration through the early administration of increased amounts of appropriate fluids available in the home, and ORS solution, if on hand
- Continue feeding (or increase breastfeeding) during, and increase all feeding after, the episode
- Recognize the signs of dehydration and take the child to a health care provider for ORS or intravenous electrolyte solution, as well as familiarize themselves with other symptoms requiring medical treatment (e.g. bloody diarrhea)
- Provide children with 20 mg per day of zinc supplementation for 10–14 days (10 mg per day for infants <6 months)

Fig. 1. WHO/UNICEF joint statement on clinical management of acute diarrhea.

Who, When, What, and How Long?

Over the past 8 years, many more studies have been published and included in analyses and reviews that further our understanding of the roles of zinc supplementation [10–14]. The latest estimates report that zinc supplementation given to children aged >6 months of age with acute diarrhea reduces the duration of the episode on average by 12 h, and by 17 h for persistent diarrhea episodes [12, 14], compared with placebo. Zinc supplements started at home also reduce hospital admissions and it is estimated that mortality due to diarrhea is reduced by 23% [15].

The safety and efficacy of zinc supplements as an adjunct treatment for diarrhea is confirmed, but there are considerable differences, referred to as heterogeneity, between the results of the trials. In some cases, the zinc supplement has a large effect and in other trials, there is no effect. We need to understand why there are these differences in order to optimize the treatment; so, what have we learned so far?

Who Should Receive Zinc Supplements?

At What Age Should Zinc Supplements Be Given? The only two studies that specifically recruited children <6 months of age [16, 17] failed to demonstrate efficacy and, currently, there is no evidence of a benefit of zinc supplements in this age group [4, 13, 14]. However, the issue is not closed because in some trials, there does seem to be benefit for younger infants. Mazumder et al. [18] ana-

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Table 1. What's new on zinc as an adjunct therapy in the management of diarrhea episodes

Who: at what age should supplements be given?	≥6 months: evidence for benefit is strong <6 months: to date, there is no evidence of benefit, but there are fewer studies and more subgroup analyses of existing data and new studies are needed as some trials do report positive effects in this age group
Where: does the strategy work everywhere?	Current recommendations do not limit use to specific populations. Although this was not explicitly investigated, there is no evidence of adverse effects in children who are not deficient. Stunting can be used as an indicator of probable zinc deficiency in order to prioritize
When: how soon after the start of an episode?	Zinc supplements are effective when started at any time during a diarrhea episode and are of proven benefit in persistent diarrhea
How long: for how many days should supplements be given?	Current recommendation is 10–14 days. In practice, programs are using 10 days as it is necessary to prescribe zinc supplements for a definitive number of days. Fewer days may also be effective but might reduce the benefits of zinc after treatment
Etiology of the diarrhea: does it matter?	Determining the cause of diarrhea episodes is unlikely to be practical. It is difficult because of multiple pathogens; potential pathogens may be found in asymptomatic people. In practice, the whole range of possible pathogens cannot be included in screening; quality control is difficult to maintain across diagnostic services. More extensive screening for diarrhea pathogens would be useful in zinc treatment trials. The efficacy of zinc in RV and other viral diarrhea episodes needs to be sorted out
Dose: what dose should be given?	The recommendation is 10 mg daily for children <6 months and 20 mg for older children. It is possible that higher doses would be effective in the younger age group and this should be tested
Safety: what's new on safety?	No serious adverse events attributable to zinc supplements have been reported despite large trials and scaled up programs in many countries. The supplements cause an increase in the numbers of children with vomiting, but this is mild, and regurgitation, which is most common with the first dose. Locally prepared preparations should be checked for acceptability
Zinc preparation: which zinc salt is best?	The soluble zinc salts gluconate, sulfate and acetate have been used successfully, but no comparative studies have been done. Sub-analysis of trials suggests that gluconate is associated with most benefit but possibly higher rates of vomiting. Trials using zinc acetate have been more likely to be negative

lyzed the subgroup of children aged <6 months in their cluster randomized community effectiveness trial in India. Caregivers in the intervention clusters were trained to give zinc in addition to ORS and the study measured the prevalence of diarrhea in cross-sectional surveys at 3 and 6 months. Compared with the control areas, the intervention areas had 40% less diarrhea. A possible explanation is the larger dose of zinc (20 mg daily compared with the usual 10 mg). A recently published trial from India [19] examined zinc supplements given as adjunct treatment to infants aged 7–120 days with probable serious bacterial infection as defined by clinical signs and a raised C-reactive protein concentration. Zinc-supplemented infants had a 40% reduced risk of treatment failure (95% CI 10–60, p = 0.0113); there was also a reduction in mortality, but numbers were small. The greatest impact was in infants who had diarrhea on admission [relative risk (RR) 0.31, 95% CI 0.14–0.65]. If these results were confirmed by other studies, this would lead to a change in notions of the efficacy of zinc supplements in young infants.

Where in the World Should Zinc Supplements Be Given?

A wide number of different locations are included in studies of zinc in diarrhea treatment and geographical location does not explain the heterogeneity. However, it is notable that the only trial from Africa (Nigeria) included in the most recent meta-analysis was negative [20]. In general, it seems that children are most likely to benefit if they are zinc deficient. In Sachdev et al.'s [6] early studies, the benefits were seen in children with a low concentration of zinc in rectal mucosal biopsies, and in Brazil, low plasma zinc was associated with greater benefit [21]; nevertheless, me-

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ta-analyses have not confirmed that zinc status at baseline can predict outcome [13]. Zinc supplements were effective in trials in regions classified as high and medium risk of zinc deficiency but not in a trial in Poland where all the children were well nourished [21, 22, 14].

Studies that started zinc supplements during diarrhea but continued at a lower dose after recovery were shown to provide significant protection against subsequent episodes.

When to Start with Zinc Supplements?

Zinc supplementation does not have to be started at the beginning of a diarrhea episode; studies enrolling children whose diarrhea started anything from 1 to 7 days earlier have registered benefit and supplements have been successful in reducing the duration of persistent diarrhea. In fact, the reduction in duration is greater in persistent diarrhea [14]. Hospital studies tend to register greater impact of zinc, but there is no indication that this is attributable to the severity of the presenting diarrhea rather than to more accurate measurement [14].

Whereas there is agreement that zinc supplements reduce the duration of diarrhea, early studies also reported reductions in the amount of diarrhea and frequency of stools [10], but the inclusion of more recent trials has led the latest reviews to conclude that zinc supplements have no significant effect on stool frequency or fecal output [13, 14].

For How Long Should Zinc Supplements Be Given?

The WHO/UNICEF joint statement was unable to give a precise number of days of treatment with zinc and pooled analyses have not been able to address this point, although this would be helpful for programs. On the one hand, one recent community trial in Bangladesh [23] reported that 5 days of treatment with zinc were equally effective as 10 days in reducing duration and both doses were effective in reducing the incidence of diarrhea episodes over the next 3 months, but this result needs to be confirmed. On the other hand, continuing supplementation after the end of the episode has some advantages. Studies that started zinc supplements during diarrhea but continued at a lower dose after recovery were shown to provide significant protection against subsequent episodes [7] and a recent study [24] provides additional support for this strategy. The problem is that programs report that even adherence to the 10-day course is difficult to achieve [25].

Etiology of the Diarrhea

In vitro studies with human intestinal cells have shown that zinc has no effect on modifying the response to enterotoxigenic *Escherichia coli* (ETEC) diarrhea in contrast to diarrhea caused by *Klebsiella* [26]. On the other hand, zinc has been shown to enhance innate immunity against ETEC [27]. Analyses of the different pathogens isolated from children in a randomized trial in India found that zinc supplements were only efficacious in cases where *Klebsiella* spp. was isolated but had no effect on diarrhea caused by ETEC or intestinal parasites and actually increased duration in rotavirus (RV) diarrhea, especially when this coexisted with ETEC [28]. The lack of benefit in RV diarrhea is in contrast to the positive effect of zinc supplementation with or without a probiotic in RV diarrhea in Turkey [29] and in hospitalized patients in India [30]. Diarrhea caused by *Vibrio cholera* [31] and *Shigella* [32] responds to zinc. It is possible that differences in the etiology of the diarrhea episode may explain some of the heterogeneity between studies, but, clearly, further studies of pathogens isolated from diarrheal episodes and laboratory research are needed to understand the mechanisms involved in the interaction between zinc and pathogens.

Are There Any Side Effects of Giving Zinc Supplements?

Zinc supplements have been consistently shown to be safe. Safety was monitored in a large trial in hospitalized children in Bangladesh using the same criteria used for pharmaceutical drugs and no serious adverse events were reported [33].

There is an increased incidence of vomiting or regurgitation with zinc supplements [10, 11, 14], which is most common within minutes of taking the first dose [34]. Increased risk of vomiting has been consistently reported across trials and occurred in all age groups. Breastfeeding and a longer duration of diarrhea before admission were positively associated with risk of vomiting and the latter explained about 60% of the observed heterogeneity in one meta-analysis of the risk of vomiting [13]. However, in the Bangladeshi study, vomiting did not lead to increased return visits to hospital or rejection of the medicine [33].

Does the Type of Zinc Salt Make a Difference?

Three soluble salts of zinc have been used in trials, i.e. zinc sulfate, gluconate and acetate. All have been shown

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to be efficacious. There is some suggestion [13] that zinc gluconate may be the most effective, but it also causes more vomiting. Some studies have combined zinc with other potentially deficient micronutrients such as vitamin A, but this did not confer additional advantage [35]. Copper has also been added because of concern that zinc can reduce copper, but in a trial in India, there was no therapeutic benefit from the zinc supplement with or without copper [36]. Addition of zinc to ORS is not advised based on lack of benefit and the disadvantage of an uncontrolled dose given over only a short period.

What Dose of Zinc Should Be Given?

The WHO/UNICEF joint statement recommends 20 mg elemental zinc daily for children ≥6 months and 10 mg for younger children. Studies using lower doses have tended to be negative [37]. There is some suggestion that doses of 20 mg are more effective in the younger age group [18]. Some positive trials have given ≥40 mg elemental zinc [6, 20, 35] with success and without apparent adverse effects, but taken together, there is no evidence that higher doses of zinc are related to greater reduction in duration of diarrhea [14]. Higher doses may be associated with increased vomiting and one study that gave 3 mg/kg/day of zinc found a significant reduction in serum copper levels after 2 weeks of supplementation [38]. The lowest effective dose should be used and, at the moment, there is no reason to change the recommendations.

Zinc Supplementation and Mortality

Given the important contribution of diarrheal deaths to child mortality [8] and the impact of zinc supplements in reducing the duration of diarrhea, it would be reasonable to hope that zinc supplementation as part of the management of acute and persistent diarrhea would reduce child mortality. A systematic review of efficacy and effectiveness studies examined this effect. Only one study reported diarrhea-specific mortality rates and the number was fewer than 50. Four studies reported all-cause mortality, but the researchers were able to estimate hospitalization for pneumonia and diarrhea and also rates of persistent diarrhea and used these indicators to estimate impact on mortality. Using these estimates, they concluded that zinc for the treatment of diarrhea reduces diarrhea mortality in children aged 12–59 months by 23% [15].

Implementation of Zinc Supplementation

Following the initial successful clinical trials, several large-scale studies were undertaken in different parts of the world. As part of a large-scale study of zinc supplements for diarrhea in Nepal [39], an additional study group was added to allow the researchers to compare caregiver-administered zinc syrup (effectiveness) with field worker-dispensed treatment or placebo (efficacy). The caregiver group experienced similarly positive results compared with the dispensed groups and a similar 45% reduction in prolonged diarrhea.

Another effectiveness community-based cluster randomized study in Bangladesh distributed zinc plus ORS through community health workers and reported positive outcomes including a 51% reduction in mortality when accidental deaths were excluded [40].

A cluster randomized community that provided education to caregivers and ensured supplies of zinc and ORS reported a significantly lower prevalence of diarrhea in the intervention group at the 3- and 6-month cross-sectional surveys that were used to measure outcome [41]. An added bonus documented by these studies is the increased use of ORS and the reduced prescription of unnecessary antibiotics [42]. This is important not only because unnecessary antibiotics can be harmful, but also because antibiotic resistance among diarrheal pathogens is a serious and increasing problem.

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A multi-country effectiveness study dispensing zinc supplements through outpatient health facilities reported good adherence to the protocol, no change or an increase in Lo-ORS use, no increase in vomiting and a reduction in the inappropriate use of antibiotics [45].

These effectiveness studies were very encouraging, but scaling up zinc treatment of diarrhea through existing health services has been more challenging (table 2). The introduction of zinc supplements through the health services in Mali included formative research and a phased design [46]. Challenges included: (1) the caregiver's per-

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Table 2. Lessons and challenges from interventions adding zinc as adjunct therapy in infectious diseases

Lessons learned If adequately trained and motivated caregivers can be trusted to give daily supplements, they obtain the same results as with directly supervised supplements. Zinc supplementation as adjunct to diarrhea treatment is cost effective. Supply of kits including ORS and zinc is efficient and well accepted. Local production of zinc salts can be used to overcome procurement problems. Social marketing of zinc products is necessary. Both formal and informal – professional or not – health services and health providers need to be included in national strategies to introduce zinc supplementation. Addition of zinc supplementation maintains or increases ORS use and decreases prescription and use of inappropriate antibiotics.
Challenges Assuring reliable supply of suitable zinc products can be difficult, and more national and international suppliers are need. Changing caregiver behavior, the demand side of health provision, is necessary to change health provider behaviors. It is relatively easy to create awareness but more difficult to change behaviors. More attention needs to be focused on what works to change caregiver attitudes and behaviors, both a sharing of experience in the current programs and new research in different populations. Start-up costs need to be considered and this may be difficult because of competing priorities, but it is essential in order to get the Ministry of Health fully engaged.
More information is needed … On the role of zinc added to standard therapy in the management of lower respiratory infections, especially in countries outside Asia. On the effect of zinc supplements on appetite (as perceived by caregivers), on dietary intake during and after infections, and on post-illness weight recovery. This would provide the basis for possible motivational messages. On zinc salts: studies need to define if there are significant differences between zinc salts and which has a better efficacy-safety profile, what is the minimal number of days of administration needed, and what are the optimal doses. On zinc in the management of tuberculosis and other infectious diseases of public health importance.

ception of diarrhea – in contrast to malaria – as a mild illness for which local remedies already exist, and (2) the confusion with malaria when diarrhea infections were accompanied by fever. Childhood illnesses often present with more than one symptom, for instance diarrhea and fever or diarrhea and cough, and this has to be taken into account [47]. A post-project survey of a large-scale zinc promotion project in Nepal (POUZN) and the final report of the multi-country initiative also highlight the need to change caregiver attitudes, the demand side of the provider-client relation [47, 48]. Other large-scale programs have tested other strategies such as diarrhea treatment kits including zinc supplements in Cambodia [49].

These large-scale programs have integrated public and private resources and used social marketing to create awareness and acceptance by government and influential medical groups, health providers and caregivers. Some programs have successfully instigated local production and overcome the hurdles of licensing laws, and/or provided zinc together with Lo-ORS in convenient forms of inclusion [49]. They have provided extensive training and engaged both the formal and informal health sector. They report many successful experiences, especially on the supply side, and they provide invaluable experience on how to achieve scale-up. It has been possible to create awareness of zinc plus Lo-ORS therapy, but in all cases where it has been measured and reported, the change in first-line health provider and caregiver behavior has been disappointing. Caregivers demand curative treatment and there is a general reluctance in these providers to shift from often ingrained treatment with antibiotics and, if available, 'antidiarrheal' medicines to the new zinc tablets or syrup. This demand-driven behavior often undermines sensitization and training.

Caregivers demand curative treatment and there is a general reluctance in these providers to shift from often ingrained treatment with antibiotics to the new zinc tablets or syrup.

These lessons and the experience of other initiatives help understand why, despite the proven benefits, the transition to programmatic interventions and nationwide scaling up of zinc plus Lo-ORS uptake has been disappointingly slow [50, 51]. The barriers to implementing national programs include problems of procurement and quality control, initial financing, implementing training and retraining at a national level and the need for more operational research [12, 50]. Some of these barriers have been overcome in recent programs, but the most resistant barriers – convincing health service providers including health professionals, traditional health providers, pharmacists and medicine vendors to adopt new treatments and caregivers to change attitudes and behavior, especially with respect to duration of treatment and the demand for curative medicines – still remain.

Zinc supplements do not immediately stop diarrhea and the reduction by about half a day in diarrhea duration, although highly significant in public health terms, is not necessarily perceived by caregivers who are anxious for cessation of symptoms. Despite extensive formative research and social marketing for behavior change, it seems that we have yet to convince mothers. Maybe messages that focus more on other perceived and/or real benefits of zinc therapy, such as increased appetite, overcoming the negative nutritional cost of diarrhea episodes, and building stronger children, will have more success. Formative research from Bangladesh identified that caregivers considered the ability to strengthen the child against further illness as an important attribute of zinc [25].

Zinc as Adjunct Therapy in Other Infections

This review has given most attention to zinc as an adjunct to diarrhea treatment, but zinc supplements work at least in part by enhancing immune responses and they might be expected to have an effect in the treatment of other infections (table 2). Pneumonia is responsible for most child deaths worldwide [8] and thus has been a focus of interest, although there are considerably fewer trials of zinc in pneumonia treatment and even fewer in other infectious diseases compared with the publications on diarrhea.

Overall, studies have concluded that there is not enough evidence at the present time or that no benefit had been shown for adding zinc supplements to standard treatment for pneumonia or lower respiratory tract infections [4]. Of the five trials identified, all in South Asia, two [52, 53] provided information on an analysis of hospitalization and tachypnea. Overall, there was a benefit of zinc with approximately 15% reduction in both variables, but this was not statistically significant.

A combination of zinc and vitamin A was shown in one study to reduce the time to clearance of *Mycobacterium* in sputum with tuberculosis [54], but subsequent studies using zinc alone have not demonstrated any benefit [55].

The older the child the greater the effect of zinc supplements. Zinc gluconate appeared to be most effective and results most homogeneous.

Zinc Supplements and the Prevention of Diarrheal Illness

Many of the early trials of oral zinc supplementation started during the acute episode but continued with a lower dose of supplement for usually 6 months. The Zinc Investigators' Collaborative Group [56] assessed the effect of preventive zinc supplementation in these studies. They reported pooled odds ratios of 0.82 (95% CI 0.72–0.93) for diarrhea incidence, of 0.75 (95% CI 0.63–0.88) for diarrhea prevalence and of 0.59 (95% CI 0.41–0.83) for pneumonia, but there was heterogeneity among the results. Further trials followed these encouraging results and there have been several meta-analyses and reviews [57–59]. Brown et al.'s [57] extensive meta-analysis demonstrated that the overall reduction in incidence of diarrhea was 20%, but that this was limited to children >12 months of age, in whom the reduction was 27%. They found no effect on the duration of episodes. Two later meta-analyses confirmed the positive findings: Yacoob et al. [60] reported an overall significant reduction of 13%, and Patel et al. [61] a 9% reduction in diarrhea incidence.

All meta-analyses have reported heterogeneity. Patel's group [61] undertook an extensive analysis to understand what was responsible for this wide variation between trial results. From the point of view of guidance for prioritizing the benefit of interventions, they reported, as in a previous analysis, that the older the child the greater the effect of zinc supplements. Zinc gluconate appeared to be most effective and results most homogeneous [61], but it should be born in mind that this salt has also been associ-

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ated with more vomiting. Zinc sulfate was also effective, but the results were variable and the five trials using zinc acetate did not have a positive effect. No trials have compared different zinc salts. Trials administering zinc supplement for <10 or >26 weeks did not show significant benefit.

In terms of expected benefit, Patel et al. [61] reported an overall reduction of 19% (effect size 0.81, 95% CI 0.75–0.88) in diarrhea prevalence, 11% reduction in incidence of persistent diarrhea (effect size 0.89, 95% CI 0.73–1.09), and 11% for dysentery (effect size 0.89, 95% CI 0.75–1.06). They also reported a potentially important and statistically significant reduction of 31% in occurrence of ≥2 diarrhea episodes in a subgroup of three trials.

All meta-analyses have shown considerable heterogeneity that has not been fully explained. Earlier trials have mostly contributed the positive results, and Patel et al. [61] observed a smaller or no effect in more recent trials. In part, this is due to the inclusion of a wider range of countries. Most – but not all – Asian trials have been positive, whereas most trials from other regions are negative. Lower- and middle-income countries reported the greatest benefit compared with the poorest and relatively rich countries.

This heterogeneity across trials, which is also seen with zinc therapy for diarrhea, has not been fully explained. Possible explanations may lie in the different pattern of etiology of diarrhea which varies with the age of the child and the environmental conditions in which they live. Despite poverty, food insecurity, high burden of disease and dietary deficiencies, studies of zinc deficiency in Africa have not so far shown significant benefit. Asia stands out as having the highest rates of low birth weight and wasting, and stunting levels are also the highest. Maternal malnutrition is also prevalent. Clearly, more research is needed to understand why some populations benefit more than others and whether maternal nutrition plays a role that is not yet fully understood.

Zinc Supplements and Prevention of Other Infections

The pooled analysis of early trials reported a very large reduction of 41% (odds ratio 0.59, 95% CI 0.41–0.83) in the incidence of pneumonia [56]. Brown et al.'s [57] meta-analysis reported a smaller, but nevertheless statistically significant and public health-significant, reduction of 15% in the incidence of acute lower respiratory infections. The effect was greater, namely 21%, when only those studies counting respiratory rate or physician diagnosis were included. The greatest effect was seen with children who were initially stunted (height for age <–2 SD). In this case, age was not a factor. A subsequent meta-analysis [58] reported a 19% reduction in pneumonia (RR 0.81, 95% CI 0.73–0.90) using the same clinical diagnosis.

Studies have also looked at the impact of zinc supplements on the prevention of malaria and, although one trial reported a reduction, others have been negative. A recent review [58] concluded that preventive zinc supplementation had no effect on incidence or mortality due to malaria.

Studies suggest that providing zinc supplements to young children who are likely to be zinc deficient could reduce infectious disease morbidity and mortality.

Prevention of Zinc Deficiency and Child Mortality

Diarrhea is responsible for 14% of deaths and pneumonia for 14% of deaths in under-5 children. If zinc supplements reduce the burden of these infections, one would expect to see a reduction in child mortality. The halving of accidental deaths in a trial in Bangladesh has already been mentioned [42]. Brown et al.'s [57] meta-analysis included thirteen comparisons and included three very large studies from Tanzania [58], Nepal [59] and India [62]. The overall RR of mortality was a statistically insignificant 0.94 (95% CI 0.86–1.02), but when the results of the three large studies were pooled and stratified by age and the comparison restricted to zinc versus placebo, there was a significant 18% reduction in total mortality (RR 0.82, 95% CI 0.70–0.96) in children >12 months of age [57]. There was no reduction in mortality in children <12 months old. However, Brown et al. [57] also comment on three studies that enrolled low-birth-weight infants and all found significant reductions in mortality in the zinc-supplemented groups. Two more recent reviews [60, 61] conducted meta-analyses of mortality and both reported a statistically insignificant reduction of about 10% in all-cause mortality. Patel et al.'s [61] results graphically illustrate the large difference between trials reported before 2006 and afterwards, with all the positive effects being reported before 2007, although not necessarily from Asia. Yacoob et al. [60] analyzed disease-specific

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Table 3. Options for strategies for preventive zinc supplementation

Strategy	Pro	Con
Zinc and/or multi-micronutrient supplements dispensed through the community or health services	Proven efficacy in clinical trials. Weekly supplements may be efficacious	Interaction between micronutrients, requires giving of 'medicine' daily – difficult to sustain. Most experience has been gained in trials (efficacy and effectiveness)
Zinc and Lo-ORS for treatment of diarrheal episodes	Reduction of subsequent diarrheal episodes. Complementary with other strategies as the most vulnerable children (most diarrheal episodes) receive most zinc	Current evidence does not support benefit in <6-month-old children. Despite proven effectiveness, scaling up to national level has been slow and compliance is variable
Fortified complementary foods distributed in programs or private sector	Processed foods, especially when ASF are included, have good zinc bioavailability. Milk is an effective vehicle, fortified drinks have been successful	Cereal-based mixes often have low bioavailability and no impact on zinc nutrition. ASF inclusion increases cost. Social marketing needed but not always effective
Fortified staple foods	Now feasible, for example wheat, rice, fish sauce	Children may not eat enough of the staple. Presence of phytates reduces bioavailability. Monitoring of industrial fortification is difficult
Biofortification of staple foods	Various strategies are available to increase zinc content of staple foods	Trials are underway, but results are not yet known. Children may not eat enough of the staple foods
Home-based fortification with multi-micronutrients (sprinkles)	One study has reported reduction in diarrhea. Good acceptance and compliance is possible. The main effect has been on anemia. Cost effective	Very few studies on impact on zinc nutrition or morbidity exist and results are variable. Efficacy is not yet proven. Acceptance is not assured – novel concept
Household techniques to increase zinc bioavailability	Soaking, germination, fermentation reduce phytates. May be effective if already part of normal food preparation. May be combined with dietary diversification to enhance effect	Acceptance in areas where practice is not common is not known – requires behavior change. Methods may not be enough to reach sufficient levels of bioavailable zinc
Dietary diversification – addition of ASF	Some positive experiences exist using locally available ASF. Additive effect with other strategies	Cost, availability and cultural acceptance of ASF may be barriers. Few studies have been performed

ASF = Animal source foods.

mortality and applied CHERG (Child Health Epidemiology Reference Group) rules [63] which discriminate in favor of high-quality evidence. Using this methodology for disease-specific mortality, they concluded that the reduction of 13% for diarrheal deaths indicated a protective effect of zinc that was of public health importance. Including children independent of whether they also had iron and folic acid supplements resulted in a reduction of 20% in pneumonia-specific mortality (RR 0.8, 95% CI 0.67–0.96).

Scaling Up the Prevention of Zinc Deficiency

These studies suggest that providing zinc supplements to young children who are likely to be zinc deficient could reduce infectious disease morbidity and mortality. Brown et al. [57] discuss the options for delivery. Children aged >1 year from populations with a higher prevalence of stunting, or who have repeated episodes of diarrhea, are those at greatest risk of zinc deficiency, but these children are also at risk of other micronutrient deficiencies, particularly iron deficiency. Iron deficiency anemia is very common and also has lifetime consequences on children's

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development. It therefore makes sense to look for strategies that offer a single option to prevent both deficiencies.

Various forms of multi-micronutrient preparations have been developed and tried in large-scale studies, but the most promising options that are currently being promoted are home-based fortification using multi-micronutrient powders, lipid nutrient supplements, food fortification, and dietary diversity, improving the diet. A complete analysis of the different strategies to provide multi-micronutrients to young children is beyond the scope of this paper, but table 3 provides a summary of the relative merits of the different strategies. This is a burgeoning area of program development, and both efficacy and implementation research over the next years will provide us with a better idea of the scope of benefit.

Conclusions

Zinc supplementation as adjunct therapy in diarrhea has been shown to be efficacious with a potential to reduce morbidity and mortality especially among populations with a high burden of zinc deficiency; more information is needed, however, to understand disparate findings and ensure that the large-scale programmatic interventions can meet the high expectations.

Preventive zinc supplements have been shown to reduce morbidity and mortality in young children, but recent trials have shown that the benefits are not universal. It is not clear whether there are benefits for children <1 year of age.

Zinc deficiency should be addressed in the context of other health and nutrition programs designed to ensure that all children meet their essential nutrient needs.

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