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Review

Zinc supplementation in young children: A review of the literature focusing on diarrhoea prevention and treatment

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SUMMARY

Background & aims: It is estimated that zinc deficiency is responsible for 4.4% of childhood deaths in Africa, Asia, and Latin America. This review examines the impact of zinc supplementation, administered prophylactically or therapeutically, on diarrhoea.
Methods: Relevant published articles were identified through systematic searches of electronic databases. Bibliographies of retrieved articles were examined.
Results: A total of 38 studies were included in this review, 29 studies examined the effect of prophylactic zinc and nine studies examined the effects of therapeutic use of zinc for treatment of diarrhoea in children under five years.
Conclusion: Prophylactic zinc has been shown to be effective in decreasing both prevalence and incidence of diarrhoea, reducing respiratory infections and improving growth in children with impaired nutritional status. There is less conclusive evidence of reduction in diarrhoea duration or diarrhoea severity. While prophylactic zinc decreases mortality due to diarrhoea and pneumonia, it has not been shown to affect overall mortality.
Therapeutic use of zinc for the treatment of diarrhoea in children has been shown to reduce diarrhoea incidence, stool frequency and diarrhoea duration as well as respiratory infections in zinc deficient children. However, stool output is only reduced in children with cholera. Less conclusive evidence exists for therapeutic zinc reducing mortality due to diarrhoea and respiratory infections. Specific definitions of diarrhoea severity, respiratory infection in further studies as well as examination of prophylactic zinc effectiveness in diarrhoea duration and severity effectiveness of therapeutic zinc in reducing mortality due to diarrhoea and respiratory infections are warranted.

1. Introduction

In humans, zinc is a vital micronutrient essential for protein synthesis, cell growth, and differentiation. Zinc is also a pro-antioxidant and anti-inflammatory agent [1]. Dietary deficiency of zinc is common in several parts of the world, particularly low income countries and low income populations in the United States. It is estimated that inadequate zinc intake affects up to a third of some populations in Southeast Asia and sub-Saharan Africa, with children and pregnant women being most severely affected [2,3]. It is estimated that zinc deficiency is responsible for over 400,000 child deaths in Africa, Asia, and Latin America every year [4].

In May 2004, the World Health Organization (WHO) and the United Nations Children's Emergency Fund (UNICEF), released a joint statement advocating oral zinc to decrease diarrhoea deaths in the world's most vulnerable children based on the evidence that oral zinc treatment reduced diarrhoea duration and severity in children with diarrhoea aged six months to five years. While over 45 countries included zinc in diarrhoea management policies, few countries have implemented effective programs and very few children are currently being appropriately treated [5].

Zinc, administered either prophylactically or in the treatment of diarrhoea has been extensively examined in the last five years. However, meta-analysis and systematic reviews of studies examining the role of zinc in the prevention and treatment of diarrhoea

Abbreviations: WHO, World Health Organization; UNICEF, United Nations Children's Emergency Fund; LBW, low birth weight; RDA, recommended dietary allowance.

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[6] had limited information on impact of dose and form of zinc and no discussion on potential mechanisms of action. While the effects of zinc supplementation in respiratory infections and mortality were discussed, the effects on growth were not included. There are no guidelines for implementation and cost-effectiveness of intervention strategies for reducing zinc deficiency that could be used by governments or other implementing agencies.

This review will summarize the data from human intervention studies that have administered zinc either prophylactically or therapeutically to treat diarrhoea and examined outcomes on respiratory infections, otitis media, anthropometric measurements and mortality in children under five years of age. Potential mechanisms of action, impact of dose for the prevention and treatment of diarrhoea and criteria to identify zinc deficiency will be highlighted. Findings from relevant reviews examining this topic will also be summarized.

2. Methods

2.1. Search strategy

We searched the following electronic databases: MEDLINE, Science Direct and EBSCO. All databases were searched from the earliest available date up until May 2012. A combination of key words addressing "zinc supplement*" or "oral zinc" and "infants" or "children" were used. Reference lists of short-listed articles for other relevant studies were further examined.

2.2. Inclusion criteria

Studies were included if:

- There was a control group not receiving zinc supplementation
- Included children from birth to 5 years old
- Participants received zinc supplementation either for treatment of diarrhoea or for prevention of diarrhoea
- Outcomes of interest were reported: diarrhoea outcomes (prevalence, incidence, stool output), respiratory infections, otitis media, anthropometric measurements and mortality

2.3. Data extraction

Data extracted from each eligible study included the following variables: study context, study design, intervention specifics and outcome effects.

3. Results

A total of 38 studies were included in this review. The effect of prophylactic zinc was examined in 29 studies; 14, 7, 1 and 18 examined diarrhoea outcomes, respiratory diseases and pneumonia outcomes, otitis-media outcomes and anthropometric measurements, respectively.

Nine studies examined the effects of therapeutic use of zinc for treatment of diarrhoea; 9, 3 and 1 examined diarrhoea outcomes, respiratory infections outcomes and mortality.

3.1. Prophylactic effects of zinc

3.1.1. Diarrhoea

In 2008, it was estimated that over 1.3 million of the 8.8 million child deaths worldwide were caused by diarrhoeal diseases [7]. The primary cause of diarrhoea among infants worldwide is viral gastroenteritis caused by rotavirus. Other causes include bacterial pathogens such as *Vibrio cholerae*, *Shigella*, and *Salmonella* and *protozoa* such as *Cryptosporidium parvum* and *Giardia lamblia* [8].

There are 28 studies included in this review examining the effect of prophylactic zinc; 9 of the 14 which examined prevalence and incidence of diarrhoea showed positive effects of prophylactic zinc, although one showed positive effects only in stunted children [9], one only in children older than 11 months [10], and one only in boys [11] (Appendix 1 online). One study conducted in South Africa did not show any benefit of prophylactic zinc in diarrhoea in children. Prevalence of stunting and wasting in study populations may explain the disparate findings. Trials in regions with high prevalence of stunting and/or wasting such as Bangladesh [12–14] and India [15–17] are more likely to show benefits of zinc supplementation to entire study populations. On the other hand, trials in regions with lower prevalence of stunting and wasting such as South Africa did not report any differences [18] in the prevalence or incidence of diarrhoea in children receiving prophylactic zinc or reported benefits only to malnourished subgroups [9,19].

Difference between male and female responses to zinc supplementation, often in opposite directions for diarrhoeal diseases has been suggested by other authors but had never been systematically analysed [11]. When prophylactic zinc was administrated to urban children of low socioeconomic status aged six to 35 months in India, incidence and prevalence of diarrhoea was 26% and 35% lower in boys compared to girls (17% and 19%), respectively [10].

Diarrhoea results from an imbalance of absorption and secretion of ions and solute across the gut epithelium, followed by the movement of water in an attempt to restore the appropriate ion concentrations. Often, this imbalance is caused by the presence of bacteria that secrete toxins that disturb the organization of the epithelium. Although a number of factors, including genetic mutations, hormonal alterations, radiation injury and mal-absorption, can cause diarrhoea, the most common cause is infection by bacterial pathogens and the subsequent release of bacterial toxins. Such toxins typically trigger signalling molecules such as cyclic AMP or intracellular Ca^{2+}, which, in turn, activate cellular Cl^- channels leading to an increase in secretion of Cl^- and consequently water. Cl^- absorption can also be affected. Increased secretion and decreased absorption of Cl^- have the same net effects on luminal Cl^- concentrations. Attenuation of Na^+ absorption can also cause diarrhoea. In addition, a single layer of contiguous cells executes the vectorial transport of ions and solutes across the apical and basolateral surfaces of the intestinal epithelium. Gross alterations in homeostatic functioning of the intestinal epithelium, such as loss of the epithelial monolayer by mechanisms including apoptosis and delayed wound repair, are likely to result in unregulated fluid loss and consequent diarrhoea. Finally, the innate immune response has a significant role in the development of diarrhoea: First, the innate immune response is important for the maintenance of intestinal homoeostasis and controlling the commensal flora. Second, innate immune responses interfere with colonization by pathogenic organisms. Third, several pathogens stimulate the recruitment and transmigration of neutrophils into the intestinal lumen. Neutrophils attached to the apical side of epithelial cells release 5′-AMP, which is converted to adenosine in the lumen [20].

Cytokines are the hormonal messengers responsible for most of the biological effects in the immune system, such as cell mediated immunity and allergic type responses. T lymphocytes are a major source of cytokines. These cells bear antigen specific receptors on their cell surface to allow recognition of foreign pathogens. There are two main subsets of T lymphocytes, distinguished by the presence of cell surface molecules known as CD4 and CD8. T lymphocytes expressing CD4 are also known as helper T cells, and these are regarded as being the most prolific cytokine producers. This subset can be further subdivided into Th1 and Th2 and the optimal scenario seem to be that humans should produce a well-balanced

Th1 and Th2 response, suited to the immune challenge. Zinc supplementation seems to affect the balance between Th1 and Th2 responses and males and females have different Th1 and Th2 responses to a variety of infections [11].

Studies including children younger than 12 months aged being breastfed [10,21,22] or including broad age range [15,16] and lack of stratification by age may have precluded finding positive effect of prophylactic zinc.

Overall, the studies examined in this review show that doses between 3 and 20 mg/d of zinc supplementation produce positive effects in children aged six months and older. It seems that a balance between nutritional status, age and dose is needed to achieve maximum benefits of prophylactic zinc. The magnitude of the increase in zinc absorption is progressively less with higher doses [23] and high doses of zinc have been found to have a negative effect in young children due to inducing some vomiting [11]. The greatest effect of supplemental zinc in reducing diarrhoea incidence among children aged 12–30 months occurred among the children in the youngest age tertile and doses of 3 mg/d and 7 mg/d were more effective than doses of 10 mg/d [24].

Other reviews and meta-analysis examining the impact of prophylactic zinc administered to children have been shown to reduce the incidence of diarrhoea [25–27]. No reduced risk of diarrhoea was found in a systematic review [28] including three trials from developing countries with breastfed LBW infants receiving zinc supplements for at least 14 days introduced within one month of birth.

There is less conclusive evidence that prophylactic zinc reduces either the duration or severity of diarrhoea episodes. The only study [11] identified in this review examining zinc supplementation on diarrhoea duration found shorter episodes of diarrhoea in boys, but not girls, receiving prophylactic zinc. As discussed above, the innate immune response has a significant role in the development of diarrhoea including the maintenance of intestinal homeostasis and controlling the commensal flora; interfere with colonization by pathogenic organisms and stimulation of the recruitment and transmigration of neutrophils into the intestinal lumen by several pathogens. Neutrophils attached to the apical side of epithelial cells release 5′-AMP, which is converted to adenosine in the lumen [20]. Zinc supplementation seems to affect the balance between Th1 and Th2 responses [11]. In addition, males and females have different Th1 and Th2 responses to a variety of infections [11].

3.1.2. Respiratory infections and pneumonia

In 2008, pneumonia caused over 1.5 (18%) of million deaths among children younger than five years [7] more than 90% of those deaths occurred in low income countries [12].

The effect of prophylactic zinc in respiratory diseases and pneumonia are inconsistent. Of eight studies assessing the effects of prophylactic zinc in respiratory diseases included in this review, four [12,13,29,30] found positive effects, one study [11] found positive effects only in girls (Appendix 1 online) and three studies [14,18,31] found no effects of prophylactic zinc in respiratory disease. One study examined the effects of prophylactic zinc in pneumonia and found no benefits [32]. It is unlikely that the children included in this study [32] examining pneumonia were zinc deficient because more than 80% of the children with a mean age of 11 months were breastfed.

Differences in the nutritional status, particularly zinc status may also explain some of the inconsistency in respiratory infections. Another explanation for the inconsistency in the effect of prophylactic zinc in respiratory infections is the variation in the lower respiratory infections case definitions used as outcomes. When lower respiratory infections case definitions were more specific, use of prophylactic zinc was more likely to lead to positives effects. For example, there was no effect in one study [14] when acute respiratory infection was defined less specifically (presence of cough or sore throat, with or without fever or coryza). On the other hand reduction of respiratory infections were observed when upper respiratory tract infection was more specifically defined (consisting of cough, rhinorrhoea, and fever without tachypnoea) [12]. As summarized by Prasad [6], zinc acts as pro-oxidant, protects and maintains the integrity of the respiratory epithelium. Zinc can also attenuate respiratory disease pathogenesis by modulating pro-inflammatory cytokine production. Finally zinc may have pathogen-specific effects but more studies are needed to investigate the effects of zinc on respiratory infections susceptibility by host-disease or pathogen-related factors.

Zinc was shown to reduce incidence of respiratory infections in two reviews [33,34] and two meta-analysis [26,35] and of pneumonia in two reviews [27,36] and one meta-analysis [25]. There was no decrease in incidence of acute respiratory infections in a systematic review [28] that included breastfed low birth weight (LBW) infants receiving zinc supplements for at least 14 days introduced within one month of birth. It is likely that infants within one month of birth were being breastfed and therefore not zinc deficient enough to benefit from zinc supplementation. Prophylactic zinc was found to have greater impact on lower respiratory tract infections in studies that enrolled more stunted children [33].

In summary, prophylactic zinc seems to reduce respiratory infection in children who are presumptively zinc deficient and when respiratory infections are specifically defined. For example, when lower respiratory infections case definitions were more specific, use of prophylactic zinc was more likely to lead to positives effects.

3.1.3. Otitis media

Otitis media is an inflammation of the middle ear, usually caused by infection. It affects people of all ages, but is particularly common in young children. Around 164 million people worldwide have long-term hearing loss due to otitis media, 90% of them in low income countries [37].

Prophylactic zinc was associated with a reduction in the incidence of otitis-media in the only study included in this review which was conducted in Bangladesh and included children aged two to 12 months [12]. However, a systematic review [37] showed mixed results for the impact of prophylactic zinc on otitis media. One community trial including children aged two to six months reported a lower incidence rate of diagnosed otitis-media with prophylactic zinc use compared with placebo. On the other hand, two community trials with children aged six to 36 months found no difference in the number of children with at least one episode of definite otitis media or in the numbers experiencing more than one definite episode between zinc and placebo groups. If we can, indeed, generalize from these experiences, it seems that prophylactic zinc is effective in children younger than six months but not in older children, which is contrary to the effects seen for diarrhoeal and respiratory infections.

Girls receiving prophylactic zinc had fewer eye and ear infections whereas boys had more ear infections [11]. As discussed above, zinc supplementation seems to affect the balance between Th1 and Th2 responses and males and females have different Th1 and Th2 responses to a variety of infections [11].

3.1.4. Anthropometric measurements

The effects of prophylactic zinc on anthropometric measurements among young children are inconclusive (Appendix 1 online). Eighteen studies examined prophylactic zinc effects on growth; 13 studies included children born with adequate birth weight

(2500 g–4000 g) [38]. Differences in the nutritional status, particularly zinc status may explain some of the findings.

Among the LBW or small for gestational age or preterm, three studies [39–41] found positive effects of the prophylactic zinc suggesting that prophylactic zinc may improve anthropometric measurements only when zinc is likely to be deficient.

One meta-analysis [42] and one review [43] including studies conducted in low middle income countries in children up to 5 years found positive effects of prophylactic zinc on anthropometric measurements.

On the other hand, a systematic review [28] did not find adequate convincing evidence of the benefits in growth in order to recommend zinc supplementation for LBW newborns in developing countries. However, the study population included LBW infants who were exclusively or predominantly breastfed at the initiation of intervention and therefore unlikely to be zinc deficient. As discussed above, infants are able to obtain adequate zinc from breast milk, even when maternal stores are suboptimum.

3.1.5. Mortality

It is estimated that in 2008, 68% of the 8.8 million deaths in children younger than five years worldwide was caused by infectious disease with the largest percentages due to pneumonia (18%), diarrhoea (15%), and malaria (8%) [7]. Other causes of deaths among children younger than 5 years of age included neonatal complications (36%) including pre-term, birth asphyxia and others, other infections (9%), other non-communicable diseases (4%), injury (3%), meningitis (2%), pertussis (2%), AIDS (2%) and measles (1%) [7]. There was no effect of prophylactic zinc on overall mortality of children in two studies included in this review [31,44]. Zinc provided to 42,546 children in Tanzania aged one to 36 months and continued till they were 48 months old did not result in a significant reduction in overall mortality [44]. Tielsh et al. [31] also found no statistically significant reduction in mortality among 21,274 children aged one to 35 months receiving daily doses of zinc compared to the 20,968 control children. Zinc concentration was unrelated to all-cause mortality in a study of 29,744 live births [45] conducted in Bangladesh to examine whether zinc, found naturally in drinking water, reduced infant deaths within one year of birth. There were 934 deaths over two calendar years. No effect of prophylactic zinc in mortality has also been found in systematic reviews including children younger than 12 months [31] or those in developing countries aged 3mo–5y [27]. In summary, the findings from these studies showed that prophylactic zinc does not seem to affect overall mortality.

On the other hand, there seems to be an effect on specific-causes mortality with prophylactic zinc. Diarrhoea mortality was reduced in several studies [12,15,16,22,24] administrating prophylactic zinc to children and also in one study [45] where high zinc levels were found naturally in drinking water. A systematic review including children aged 3mo-5y in developing countries showed reduction in diarrhoea mortality by 13% due to prophylactic zinc [27]. Prophylactic zinc reduced mortality due to pneumonia in two studies [12,15] and in one systematic review including children aged 3mo-5y in developing countries by 15% [27].

In summary, prophylactic zinc seems to be effective in decreasing the prevalence and incidence of diarrhoea in children with impaired nutritional status. It is very likely that impaired nutritional status of the children is related to insufficient intake of nutrients including zinc and therefore the prophylactic use of zinc could be considered a nutritional intervention. Male and female responses to prophylactic zinc are different. Doses between 3 and 20 mg/d of zinc supplementation have been shown to produce positive effects in children aged 6 months and older. It seems that a balance between nutritional status, age and doses is needed to achieve maximum benefits of prophylactic zinc. There is less conclusive evidence that prophylactic zinc reduces either the duration or severity of diarrhoea episodes. Prophylactic zinc also seems to be effective in reducing respiratory diseases and in improving anthropometric measurements in children older than 6 months in populations where zinc is deficient for example when breastfeeding is not adequate and when respiratory tract infection is specifically defined. There is limited evidence that prophylactic zinc decreases otitis media in children younger than 6 months. Prophylactic zinc seems to improve anthropometric measurements in zinc deficient children. Prophylactic zinc does not seem to affect overall mortality but seems to reduce diarrhoea mortality and pneumonia mortality.

3.2. Therapeutic zinc effects

3.2.1. Diarrhoea

Nine studies examining the effects of therapeutic use of zinc for treatment of diarrhoea met the inclusion criteria of this review (Appendix 2 online).

Four studies examined the effects of therapeutic use of zinc on the incidence of diarrhoea. Incidence of recurrent diarrhoea was reduced in three studies [46–48] and did not change in one study [49]. The higher serum zinc level in the placebo group compared to the intervention group at baseline may have [49] limited any benefit of zinc supplementation on incidence of diarrhoea The levels of zinc serum were similar in the intervention and control groups at the end of the supplementation period of 2 weeks [49]. A systematic review showed no benefit of zinc used for the treatment of diarrhoea and no reduction in the incidence of persistent diarrhoea ($\geq$14 d pre-enrolment duration), dysentery or mortality [50]. The authors of the review [50] suggest that baseline zinc levels may not be representative of the existing zinc deficiency state. As discussed above, if children are not zinc deficient, zinc supplementation is unlikely to produce any benefits. In summary, it seems that therapeutic use of zinc decrease incidence of diarrhoea in zinc deficient children.

Contradictory effects on severity of diarrhoea have been reported when zinc is used in the treatment of diarrhoea. The definitions used for diarrhoea severity vary across studies; most commonly used are stool output, stool frequency and diarrhoea duration. Diarrhoea severity has also been indicated by more than three episodes of some dehydration or any episode of severe dehydration [49]. The degree of dehydration is rated on a scale of three: [51] i) mild dehydration – no signs or symptoms; ii) moderate dehydration – thirst, restless or irritable behaviour, decreased skin elasticity and sunken eyes; and iii) severe dehydration - symptoms become more severe, shock, with diminished consciousness, lack of urine output, cool, moist extremities, a rapid and feeble pulse, low or undetectable blood pressure, and pale skin.

Five of nine studies included in this review examining the effects of therapeutic use of zinc for the duration of diarrhoea found positive effects [46–48,52,53]. Zinc reduced the duration of acute and persistent episodes of diarrhoea by 16% and 24% respectively and the incidence of subsequent diarrhoea by 11% [25,54]. A reduction of 19.7% in the mean duration of diarrhoea was reported in a systematic review [50] including 32 trials. Other reviews [8,55–58] have reached similar conclusions.

Therapeutic use of zinc had no effect on diarrhoeal duration in three studies [49,59,60], while one study found a negative effect in children aged 1–5 months [61]. There was no plausible explanation for the negative effects of zinc on duration of diarrhoea but it is likely that children aged 1–5 months [61] had adequate zinc levels due to zinc transfer transplacentally or through breast milk [44] and therefore therapeutic use of zinc would be unlikely to

influence the duration of diarrhoea. Adequate zinc status is also the most likely explanation for the lack of effect in duration of diarrhoea of therapeutic use of zinc reported in the three other studies [49 59 60]. This hypothesis was corroborated in one meta-analysis [57] and one systematic review [58].

Higher risk of vomiting when receiving zinc supplementation in the treatment of diarrhoea compared to control group has been reported in a systematic review [50] and a meta-analysis [8] particularly among participants receiving zinc gluconate compared to participants receiving zinc sulphate or zinc acetate [8]. Therapeutic use of zinc may have been the cause of vomiting in 12.7% of the participants after the first dose of zinc [8].

Stool output was examined in three studies [49,53,60], one systematic review [50] and one meta-analysis [57]. The only study [53] showing benefits of therapeutic use of zinc included children aged 3–14 years old with cholera. Children with cholera [53] as well as with shigellosis [47] and with *Entamoeba histolytica* [62] were shown to have reduced frequency, duration and severity of diarrhoea.

The effects of therapeutic use of zinc on stool frequency were examined in two studies [48,59], one systematic review [50] and one meta-analysis [8] and suggest that zinc treatment is unlikely to lead to any benefits when provided to children who are unlikely to be deficient in zinc.

In summary, it seems that therapeutic use of zinc decreases incidence of diarrhoea, diarrhoea duration and stool frequency when administered to children who are zinc deficient but it does not seem to reduce stool output unless the diarrhoea is caused by cholera diarrhoea.

3.2.2. Respiratory infections and pneumonia

Three studies investigating the effects on respiratory infections of therapeutic zinc administered in the treatment for diarrhoea showed inconsistent results (Appendix 2 online). These studies have administered zinc to treat diarrhoea and examined the effects on incidence and, or prevalence of respiratory infections. One study [46] including 8070 children aged 3–59 months showed a lower incidence of respiratory infections in zinc treated children. Two other studies found no difference in the incidence, prevalence or duration of respiratory infections between the treatment and control groups. One of the studies [61] that did not find beneficial effect from zinc supplementation included children aged 1–5 months who are unlikely to be zinc deficient as children in the zinc group were more likely to be exclusively breastfed that children in the control group. The other study [48] included 154 children aged 3–24 months and 50% of the children were breastfed. This study showed that zinc treatment reduced diarrhoea and stool frequency but there was no significant difference in the incidence or duration of respiratory tract infection between the zinc supplemented and the non-supplemented group [48]. As discussed above, a possible explanation for this puzzling finding may be the less specific definition of respiratory infection used. In summary, therapeutic use of zinc seems to decrease incidence of respiratory infections when administered to children who are zinc deficient.

3.2.3. Mortality

When zinc was used for the treatment of diarrhoea, there were fewer deaths from respiratory infections among zinc supplemented children compared to control group in the only study [46] included in this review. A meta-analysis including four randomized controlled trials showed that zinc reduced the rate of treatment failure or death due to persistent diarrhoea and the benefits were stronger in children younger than 12 months, especially boys, and in children who were wasted or had low zinc levels [55]. In summary, it seems that therapeutic zinc may decrease respiratory infection mortality and diarrohea mortality.

In summary, prophylactic zinc seems to be effective in decreasing the diarrhoea prevalence and incidence, respiratory infections and improving growth in children with impaired nutritional status. There is less conclusive evidence that prophylactic zinc reduces either diarrhoea duration or diarrhoea severity. Prophylactic zinc does not seem to affect overall mortality but seems to reduce diarrhoea mortality and pneumonia mortality. Despite of being estimated that zinc deficiency accounts for over 400,000 child deaths (4.4% of childhood deaths) in Africa, Asia, and Latin America every year [4] overall mortality does not seem to be affected by zinc supplements presumably due to the scale of non-zinc dependent mortality. Zinc used for the treatment of diarrhoea in children seems to reduce diarrhoea duration, diarrhoea incidence, stool frequency and respiratory infection in zinc deficient children, but seems to reduce stool output only in children with cholera. Less conclusive evidence exists for the reduction of mortality due to diarrhoea and respiratory infection with the therapeutic use of zinc.

4. Criteria to identify zinc deficiency in a population

Mild zinc deficiency which has been often reported among low income populations does not have characteristic symptoms and there is no single and specific index that accurately reflects zinc nutritional status [63]. It has been suggested that zinc deficiency is likely to occur among populations who are iron deficient because both iron and zinc absorption are equally affected by phytate [64]. While it has been suggested that physiologic adjustments such as increased efficiency of zinc absorption, reduced zinc excretion and redistribution of tissue zinc [65] may occur in zinc deficiency, homeostatic adjustments are limited and likely are primarily limited to reducing zinc losses, not increasing efficiency of zinc absorption [66].

Population indicators of zinc status [67] can be categorized in: (1) biochemical; (2) nutritional and (3) functional. Ideally all three types of indicators would be used together to obtain the best estimate zinc deficiency risk in a population and to identify specific subgroups with elevated risk.

(1) Biochemical indicators: Plasma or serum zinc, urinary zinc concentration and hair zinc values are useful marker of zinc status [68]. Plasma zinc is more often used [12,15,25,33,54,69] with zinc deficiency defined as low when levels range from 8.1 μmol/L [63] to 9.9 μmol/L [70]. Zinc in the red cells and hair may be used for assessment of body zinc status. However, because these tissues turn over zinc slowly, their zinc levels do not reflect recent changes with respect to body zinc stores. Zinc determination in granulocytes and lymphocytes, however, reflect recent body zinc status more accurately and is thus a useful measurement. A quantitative assay of alkaline phosphatise activity in the granulocytes is also a useful measurement. Urinary excretion of zinc is decreased as a result of zinc deficiency. Thus, determination of zinc in 24-h urine may be of additional help in diagnosing zinc deficiency [6]. Zinc-fluorophores such as the Zinquin chemosensor has been used to study the role of intracellular Zn^{2+}. However there is a need for further studies to be made for biological applications related to (i) kinetic aspects, (ii) delivery into cells and how long it remains responsive to intracellular Zn^{2+}, and (iii) improvement in the fluorescence efficiency. [71]

(2) Nutritional indicators: have been suggested to identify populations who would benefit from zinc administration

[25]. A 24-h dietary recall method is a dietary method often used in large surveys due to its short administration time. During an interview, the participant tells the interviewer the quantity of foods and beverages consumed in the preceding day. The advantages are that this method has a relatively small participant burden, it does not affect the participants' food intake pattern and the collected data are more reliable due to the personal contact with the interviewer. However, the participants' recall depends on memory. There is a large within-participant day to day variation in energy intake of individuals [72]. In addition, overestimation or underestimation of the consumed amount of food increases the inaccuracy of dietary assessment using 24-h dietary recall. The 24-h dietary recall is not appropriate to measure food intake at the individual level but it is appropriate at group level [72] and could estimate prevalence of inadequate zinc intake. Risk of zinc deficiency is a public health concern when the prevalence of inadequate zinc intake is >25%.

(3) Functional indicators: Commonly used measures of growth may provide useful proxies of zinc status. A review undertaken by Fisher Walker and Black [73] confirmed the recommendation of the World Health Organization that 20% or more of stunting rate (height for age < 2 SD) is indicative of zinc deficiency at the population level for children under 5 years. Rates of underweight (weight for age < 70% of the median National Centre for Health Statistics standard) [48] and rates of iron deficiency [64] have also been suggested as an indicator of zinc deficiency among children under five years.

Because zinc deficiency is among the most important causes of morbidity in developing countries, the joint WHO/UNICEF/iZiNCG working group reviewed available indicators of population zinc assessment to identify countries and regions that are at increased risk for zinc deficiency and defined criteria for zinc intervention (Appendix 3 online) [67].

In summary, there are no characteristic apparent symptoms of zinc deficiency and no sensitive index to indicate zinc nutritional status. Growth faltering and immune impairment are characteristic of but not specific to zinc deficient, but provide useful population level proxy markers. Therefore, identification of need of zinc supplementation programs is often based on biochemical, nutritional and functional indicators for zinc deficiency.

5. Mechanism of action, doses and side effects

The exact mechanism by which zinc is an effective therapy for diarrhoea and also prevents subsequent morbidity is not clearly known. One plausible mechanism is via the important role zinc plays in maintaining proper immune function and specifically enhancing cellular immunity.

Zinc supplementation is most commonly provided as daily tablets [44]. Supplements with zinc suitable for young children are dispersible tablets or syrup [5,44]. The most common oral zinc preparations include: zinc acetate, zinc gluconate, zinc haemoglo and zinc oxide [53,69,74] but the last one is not recommended for use in children [75] as it practically insoluble and poorly absorbed [76]. According to WHO manufacturing guidelines, supplements with zinc specifically suitable for children should not contain other micronutrients that may compete for absorption [5].

The doses of zinc used in the supplements for children aged six to 59 months ranged from 0.7 to 1.8 mg/kg [25], from 1 to 21.4 mg/d [33,69], or from 15 to 140 mg as a single weekly dose [26]. Doses typically used in the trials reviewed have not been demonstrated to affect copper, and significant effect on iron is unclear. It has been recommended that doses of zinc supplements should be two to three times the recommended dietary allowance (RDA) to treat mild zinc deficiency, four to five times the RDA to treat moderate to severe deficiency and 20 mg/day to treat acute diarrhoea in malnourished children six to 36 months [44,74,75].

The joint recommendation from WHO and the UNICEF is to provide a lower osmolarity oral rehydration therapy and provide zinc treatment (10 mg/d and 20 mg/d zinc for infants less and older than six months, respectively) for children with acute diarrhoea of 10– 14 days duration [5]. Although there is concern that as zinc is not stored in the body after a large oral dose, it must be available in the daily diet [77]. Positive effects of zinc supplementation have been observed with weekly administration of zinc [16] which is beneficial and cost-effective compared to daily regimens that are not practical for long-term use [12].

There are some side effects of zinc supplements. There was an increased number of days with vomiting in the zinc group compared to the control group when zinc gluconate was administered to infants (10 mg of elemental zinc) or to children (20 mg of elemental zinc) [15] and also when it was provided as a syrup [12]. Unpleasant taste [12] of zinc has been suggested as a reason for vomiting but it is more likely to be due to zinc being a gastric irritant [78].

There is sufficient evidence for the benefits of therapeutic use of zinc in children six months to five years with diarrhoea. Since 2004, when WHO and the UNICEF released a joint statement to decrease diarrhoea deaths among the world's most vulnerable children, 66 and 46 countries have changed diarrhoea management policies to include low osmolarity oral rehydration solution and zinc, respectively [5]. However, few countries have implemented effective supplementation program and very few children are currently being appropriately treated [5]. Monitoring of a program aimed to implement zinc treatment promotion and delivery strategies in Bangladesh including household surveys of families with a child aged between 6 and 59 months showed rapid increase in awareness over the first year of the program and there was no indication of a potential fall-off of oral rehydration solution use as zinc was introduced [79]. Placing responsibility and building capacity for the production of the dispersible zinc tablet formulation within a local laboratory was found to be pivotal to moving the regulatory process forward. Likewise, gaining the support of the local paediatric association was also very important for the scale up of zinc supplementation in Bangladesh [79]. Mass media was shown to play an important role in increasing caregivers' knowledge about zinc and encouraging trial and correct use [80]. On the other hand, low adherence to standard treatment guidelines for management of acute diarrhoea in children under 12 years has also been demonstrated in India [81].

6. Conclusions

In summary, prophylactic zinc seems to be effective in decreasing the incidence of diarrhoea, in decreasing respiratory infections and in improving growth in children with impaired nutritional status. There is less conclusive evidence that prophylactic zinc reduces diarrhoea duration or diarrhoea severity. While some studies indicate that prophylactic zinc may have an impact on mortality due to diarrhoea and pneumonia, an impact on overall mortality has not been demonstrated. Zinc used in treatment of diarrhoea in children seems to reduce diarrhoea duration, stool frequency and respiratory infection in zinc deficient children, but stool output is reduced only in children with cholera. There is less conclusive evidence that therapeutic zinc reduces mortality due to diarrhoea and respiratory infections. There is no sensitive index to indicate zinc nutritional status. Use of zinc treatment to decrease

diarrhoea deaths among children is recommended by the WHO and the UNICEF. However, few countries have implemented effective programs and very few children are currently being appropriately treated. Zinc treatment has been included in diarrhoea management policies in many countries, but there are no guidelines for intervention strategies to reduce zinc deficiency at a population level. Funding for key strategies for diarrhoea management has not been sufficient and diarrhoea continues to kill over 1.3 million children each year.

Further studies should examine the effectiveness of prophylactic zinc in diarrhoea duration and severity as well as effectiveness of therapeutic zinc reducing mortality due to diarrhoea and respiratory infections among children under five years. It would also be advised for future studies to have clear definitions of diarrhoea severity and specific definition of respiratory infection.

Statement of authorship

SCL defined the design of the study, undertook the literature search, data screening, data extraction, data collation, data analysis and drafted the manuscript. GS helped with manuscript writing providing critique and overall scientific input. KM helped with manuscript writing, providing critique and overall scientific input. All authors read and approved the manuscript.

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Conflict of interest

All authors confirm that there was no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2014.08.002.

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