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**ZINC SUPPLEMENTATION AS AN ADJUVANT
THERAPY IN MANAGEMENT OF DIARRHOEA IN
CHILDREN YOUNGER THAN 5 YEARS OLD**

**HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
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DISCLOSURE

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EXECUTIVE SUMMARY

Background

Diarrhoea remains the leading cause of death among infants and young children in low- and middle-income countries. Globally, an estimated 1.87 million children less than five years of age succumbed every year to the fluid loss and dehydration associated with diarrhoea, which approximately 19% of total child deaths. African and South-East Asia regions combined contain 78% of all diarrhoea deaths occurring among children in the developing world and 73% of these deaths are concentrated in about 15 developing countries. In Malaysia, acute diarrhoea is still a major public-health concern and it is mostly under-notified.

The majority of diarrhoeal deaths are caused by dehydration that can be treated with oral rehydration solution (ORS). Development of an improved formula for ORS solution with reduced levels of glucose and salt (NaCl) shortens the duration of diarrhoea, reduces stool volume and reduces the need for unscheduled intravenous (IV) fluids. In 2004, the World Health Organization (WHO) and the United Nations Children's Emergency Fund (UNICEF), issued a global recommendation advocating oral zinc supplementation in addition to ORS to decrease diarrhoea deaths in the world's most vulnerable children based on the recent advances that the oral zinc treatment reduced diarrhoea duration and severity in children with diarrhoea aged six months to five years.

The use of zinc in treating acute diarrhoea is thought to affect immune function or intestinal structure or function and the epithelial recovery process during diarrhoea. Zinc, administered either prophylactically or in the treatment of diarrhoea has been extensively examined in the last five years. Despite the WHO recommendation, the implementation of zinc supplementation in the management of diarrhoea has not yet been possible in all developing countries.

This technology review was requested by Medical Officer and Senior Deputy Director, Perak State Health Office, Ministry of Health Malaysia to review the evidence on the use of zinc supplementation as adjuvant therapy in the management of diarrhoea in children younger than five years old.

Objective/aim

To assess the effectiveness, safety and cost-effectiveness of zinc supplementation as an adjuvant therapy in management of diarrhoea in children younger than five years old.

Results and conclusions

A total of 430 titles were identified through the OVID interface and PubMed. There were two systematic reviews (SR) and meta-analyses, one randomized controlled trial, two cost-effectiveness analyses and one cost-utility analysis were included in this review.

Effectiveness

There was good level of retrievable evidence to suggest that zinc supplementation was able to shorten the duration of acute diarrhoea by about 10 hours (mean difference -10.44 hours, 95% CI: -21.13, 0.25) although the difference was not statistically significant, and shorten the duration of persistent diarrhoea by about 16 hours (mean difference -15.84 hours, 95% CI: -25.43, -6.24). An overall 26% (95% CI: 20%, 32%) reduction in the estimated relative risk of diarrhoea lasting beyond three days was observed among zinc-treated children as well as reduction in the stool output and stool frequency. In children with signs of moderate malnutrition, the effect appears greater, reducing the duration of diarrhoea by around 27 hours (mean difference -26.98 hours, 95% CI: -14.62, -39.34). However, the evidence with regards to the benefit of zinc supplementation for children less than six months of age was unclear. Limited good level of retrievable evidence to suggest that zinc supplementation was associated with increased use of ORS and decreased use of antibiotics during acute diarrhoea. There was insufficient evidence to suggest that zinc supplementation during acute diarrhoea reduces mortality.

Safety

Good level of retrievable evidence to suggest that the use of zinc supplementation in the management of diarrhoea for children younger than five years old was safe. Most common complication reported was vomiting. However, the evidence found no difference in time to resolution of vomiting between zinc and placebo.

Cost-effectiveness

Based on the two cost-effectiveness analyses and one cost-utility analysis, zinc supplementation as an adjunct in the management of diarrhoea in children younger than five years old was found to be more cost-effective than the standard treatment. In terms of price, the price for zinc supplementation in Malaysia was unknown due to limited availability. However the price for zinc supplementation in form of syrup in Indonesia is approximately RM 10.67 per 100 ml bottle and in form of diarrhoea kit which consisted of ORS as well as 10 of 20 mg tablets of zinc sulphate in Cambodia is approximately RM 1.60 per kit.

Organizational issues

- **Hospital stay**

There was good level of retrievable evidence to suggest that zinc supplementation during acute diarrhoea was associated with reduction in the duration of hospital stay among children hospitalised for diarrhoea compared to the control groups.

- **Guidelines**

WHO and UNICEF have issued a global recommendation in 2004 which advised zinc supplementation in addition to ORS for the treatment of all diarrhoea episodes among children younger than five years of age. ESPGHAN and ESPID stated that children age more than

six months in developing countries may benefit from the use of zinc in the treatment of acute gastroenteritis. However, in the regions where zinc deficiency is rare, no benefit from the use of zinc is expected.

Methods

Literature search was done to search for published articles to assess the effectiveness, safety and cost-effectiveness of zinc supplementation as an adjuvant therapy in management of diarrhea in children younger than 5 years old. The following electronic databases were searched via OVID Interface: MEDLINE (1946 to present), EBM Reviews-Cochrane Database of Systematic Reviews (2005 to January 2016), EBM Reviews-Cochrane Central Register of Controlled Trials (December 2015), EBM Reviews–Database of Abstracts of Review of Effects (2nd Quarter 2015), EBM Reviews-Health Technology Assessment (4th Quarter 2015) NHS economic evaluation database (2nd Quarter 2015), Pubmed and INAHTA database. The last search was run on 20th January 2016.

ZINC SUPPLEMENTATION AS AN ADJUVANT THERAPY IN MANAGEMENT OF DIARRHOEA IN CHILDREN YOUNGER THAN 5 YEARS OLD

1. INTRODUCTION

Lack of safe water and inadequate sanitation in many parts of the world contribute to diarrhoea which remains the leading cause of death among infants and young children in low- and middle-income countries. Globally, an estimated 1.87 million children less than five years of age succumbed every year to the fluid loss and dehydration associated with diarrhoea, which is approximately 19% of total child deaths.¹ African and South-East Asia regions combined contain 78% of all diarrhoea deaths occurring among children in the developing world and 73% of these deaths are concentrated in about 15 developing countries.¹ Children who are malnourished or have impaired immunity are at utmost risk of life-threatening diarrhoea.² In Malaysia, acute diarrhoea is still a major public-health concern and it is mostly under-notified.³

The majority of diarrhoeal deaths are caused by dehydration that can be treated with oral rehydration solution (ORS). Development of an improved formula for ORS solution with reduced levels of glucose and salt (NaCl) shortens the duration of diarrhoea, reduces stool volume and reduces the need for unscheduled intravenous (IV) fluids.⁴ The reason behind some episodes of persistent diarrhoea is unclear, but host factors such as zinc deficiency, which may increase susceptibility to enteric infections and delay mucosal recovery, would be expected to contribute to this effect.⁵ In 2004, the World Health Organization (WHO) and the United Nations Children's Emergency Fund (UNICEF), issued a global recommendation advocating oral zinc supplementation in addition to ORS to decrease diarrhoea deaths in the world's most vulnerable children based on the recent advances that the oral zinc treatment reduced diarrhoea duration and severity in children with diarrhoea aged six months to five years.⁶

Although severe zinc deficiency is rare in humans, mild to moderate deficiency may be common worldwide. Zinc deficiency has been found to be widespread among children in developing countries, and occurs in most of Latin America, Africa, the Middle East and South Asia. The use of zinc in treating acute diarrhoea is thought to affect immune function or intestinal structure or function and the epithelial recovery process during diarrhoea. Zinc, administered either prophylactically or in the treatment of diarrhoea has been extensively examined in the last five years. Despite the WHO recommendation, the implementation of zinc supplementation in the management of diarrhoea has not yet been possible in all developing countries.^{7,8}

This technology review was requested by Medical Officer and Senior Deputy Director, Perak State Health Office, Ministry of Health Malaysia to review the evidence on the use of zinc supplementation as adjuvant therapy in the management of diarrhoea in children younger than five years old.

2. OBJECTIVE / AIM

To assess the effectiveness, safety and cost-effectiveness of zinc supplementation as an adjuvant therapy in management of diarrhoea in children younger than five years old.

3. TECHNICAL FEATURES

3.1 What is zinc supplementation?

Zinc is an essential micronutrient for protein synthesis, cell growth and differentiation in humans. Zinc is a common metallic element that can be found in a variety of foods such as meat, fish, almonds, and breakfast cereal. Zinc cannot be stored in the body and almost 50% of zinc excretion takes place through the gastrointestinal tract and is increased during episodes of diarrhoea. Young children who are regularly exposed to gastrointestinal pathogens and have diets low in animal products are susceptible to zinc deficiency. The recommended daily intake of zinc for healthy children is 3 mg to 5 mg per day for children under five years old and markedly higher for malnourished children which is 2 mg to 4 mg/kg/day.⁸



Zinc supplementation for children with diarrhoea as recommended by WHO and UNICEF, is 20 mg per day (10 mg per day for infants under the age of six months), for 10 to 14 days along with ORS and fluid, continued feeding and selective use of antibiotics. Types of zinc salt usually given are zinc sulphate, zinc acetate or zinc gluconate, which are all water-soluble compounds.⁸ Zinc supplementation during acute diarrhoea, is claimed to help reduce the duration and the severity of diarrhoea and have an additional benefit over ORS in reducing children mortality.⁸

3.2 Mechanism of action

The mechanism of action of zinc in the management of diarrhoea is not fully understood. Zinc has been known to promote immunity, skin and mucosal resistance to infection, growth and development of the nervous system. Zinc has influences on the activity of over 300 enzymes which are involved in

DNA replication and transcription. It is also a vital anti-oxidant which preserves cellular membrane.⁹ At the level of gastrointestinal system, zinc restores mucosal barrier integrity and enterocyte brush-border enzyme activity. It promotes the production of antibodies and circulating lymphocytes against intestinal pathogens and has a direct effect on ion channels.



4. METHODS

4.1 Searching

Electronic databases searched through the Ovid interface:

- MEDLINE (R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present
- EBM Reviews- Cochrane Central Register of Controlled Trials- December 2015
- EBM Reviews- Database of Abstracts of Review of Effects- 2nd Quarter 2015
- EBM Reviews- Cochrane Database of Systematic Reviews- 2005 to January 2016
- EBM Reviews- Health Technology Assessment- 4th Quarter 2015
- EBM Reviews- NHS Economic Evaluation Database- 2nd Quarter 2015

Other databases:

- Pubmed
- Other websites: INAHTA, FDA

Additional articles were identified from reviewing the references of retrieved articles. General search engine was used to get additional web based information. The search was limited to articles on human. There was no

language limitation in the search. Appendix 1 showed the detailed search strategies. The last search was conducted on 20th January 2016.

4.2 Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria

| | |
|---------------|---|
| Population | Children less than 5 years of age with diarrhoea |
| Interventions | Zinc supplementation, zinc sulphate, zinc gluconate, zinc acetate |
| Comparators | placebo, no comparator, standard treatment |
| Outcomes | Overall survival rate, mortality rate, morbidity rate, duration of diarrhoea, number of children with persistent diarrhoea, diarrhoea severity, stool output, stool frequency Complications, adverse events Cost, cost-effectiveness, cost utility, cost-analysis and economic evaluation Organizational – training, manpower, settings, hospital stay, guidelines |
| Study design | Health Technology Assessment (HTA) reports, Systematic review (SR) and Meta-analyses, SR, Randomised Controlled Trials (RCT) |

Exclusion criteria

- i) Animal study / laboratory study, other study design
- ii) Narrative review
- iii) Non English full text articles

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) checklist and evidence were graded according to the US/Canadian Preventive Services Task Force (See Appendix 2)

5. RESULTS AND DISCUSSION

A total of 430 titles were identified through the OVID interface and PubMed. There were two systematic reviews (SR) and meta-analyses, one randomized controlled trial, two cost-effectiveness analyses and one cost-utility analysis included in this review.

5.1 EFFICACY / EFFECTIVENESS

5.1.1 Zinc supplementation for treatment of acute diarrhoea

Lazzerini M et al. (2013) conducted a systematic review and meta-analysis to evaluate oral zinc supplementation for treating children with acute or persistent diarrhoea. Twenty-four randomised controlled trials enrolling 9128 children, comparing oral zinc supplementation with placebo in children aged one month to five years with acute or persistent diarrhoea, including dysentery were included in this review. Most trials were conducted in hospitals and all the trials were conducted in countries ranked as high risk for zinc deficiency, except for five trials conducted in countries at medium risk; Nepal, Turkey, Brazil, Nigeria and Poland. The zinc dose for most trials was 20 mg/ day and the type of zinc salt used were zinc sulphate, zinc acetate and zinc gluconate. Zinc was administered as syrup in most trials. Data were analysed and all results were presented with 95% confidence intervals (CI). The primary outcomes of interest were diarrhoea duration and diarrhoea severity. The secondary outcomes of interest included hospitalisation and death from any cause and diarrhoea specific.^{10 Level I}

From the analysis, it was found that there was insufficient evidence from well conducted randomised controlled trials to show whether zinc supplementation during acute diarrhoea reduces death or hospitalisation. In children aged greater than six months, six trials involving 2,175 children with acute diarrhoea found that zinc supplementation may shorten the duration of diarrhoea by about 10 hours (mean difference -10.44 hours, 95% CI: -21.13, 0.25) although the difference was not statistically significant. In six trials involving 3,865 children with acute diarrhoea, it was found that zinc supplementation probably reduces the number of children whose diarrhoea persists until day seven (relative risk (RR) 0.73, 95% CI: 0.61, 0.88). Three trials involving 336 children found that the effect appears greater in terms of reducing the duration of diarrhoea by about 27 hours in children with signs of moderate malnutrition (mean difference -26.98 hours, 95% CI: -14.62, -39.34). In children with persistent diarrhoea, five trials involving 529 children found that zinc supplementation probably shortens the duration of diarrhoea by approximately 16 hours (mean difference -15.84 hours, 95% CI: -25.43, -6.24).^{10 Level I}

On the other hand, in children aged less than six months, two trials involving 1334 children found that zinc supplementation may have no effect on mean diarrhoea duration (mean difference 5.23 hours, 95% CI: -4.00, 14.45) and in one trial involving 1074 children, zinc supplementation was found to may even increase the proportion of children whose diarrhoea persists until day

seven (mean difference -26.98 hours, 95% CI: -14.62, -39.34). The authors concluded that in areas where the prevalence of zinc deficiency or the prevalence of moderate malnutrition is high, zinc may be of benefit in children aged six months or more and that the current evidence does not support the use of zinc supplementation in children below six months of age.¹⁰ Level I

A systematic review and meta-analysis was conducted by Lamberti L M et al. (2013) with the aim to estimate the effect of oral therapeutic zinc supplementation for acute diarrhoea among children under five years of age. One hundred and four randomised controlled trials consisted of 15 non-Chinese and 89 Chinese studies, assessing oral zinc supplementation of any zinc salt in comparison to a control group receiving placebo or supportive therapy were included in this review. Included studies were conducted in sites located within 10 countries: India, Bangladesh, Nepal, Turkey, Brazil, Pakistan, Ethiopia, Yemen and Poland. The total enrolment of included studies was 6,198 zinc group and 6,039 control group diarrhoea cases. Chinese and non-Chinese studies reported the effect of therapeutic zinc supplementation on decreased episode duration, stool output, stool frequency, hospitalisation duration and proportion of episodes lasting beyond three and seven days. Pooling of the studies was done to generate global estimates of the effect of oral therapeutic zinc supplementation on selected morbidity and mortality outcomes among children under five years of age.¹¹ Level I

The review found that the results of the studies identified through non-Chinese databases showed that the acute diarrhoea episodes were 4% (95% CI: 1%, 8%) shorter in duration among children treated with zinc compared to those receiving placebo. Stool frequency was decreased by 6% (95% CI: 2%, 10%) among zinc-treated children. Zinc-treated children had a reduced relative risk of acute diarrhoea lasting beyond three days (RR 0.78, 95% CI: 0.67, 0.90) and seven days (RR 0.74, 95% CI: 0.55, 0.99). In addition, outcomes pooled across studies conducted in China showed reductions in the duration of diarrhoea, stool output and stool frequency among zinc-treated children with acute diarrhoea attributable to rotavirus and to non-specific causes. Diarrhoea duration was reduced by 37% (95% CI: 35%, 39%) among non-specific episodes and 31% (95% CI: 29%, 34%) among rotavirus episodes. The RR of diarrhoea lasting beyond three days was reduced among zinc-treated patients with non-specific (RR 0.73, 95% CI: 0.66, 0.79) and rotavirus diarrhoea (RR 0.70, 95% CI: 0.63, 0.78). Pooling Chinese and non-Chinese studies yielded an overall 26% (95% CI: 20%, 32%) reduction in the estimated relative risk of diarrhoea lasting beyond three days among zinc-treated children. The authors concluded that the studies conducted in and outside China report reductions in morbidity as a result of oral therapeutic zinc supplementation for acute diarrhoea among children under five years old and that the WHO recommendation for zinc treatment of diarrhoea episodes should be supported in all low- and middle-income countries.¹¹ Level I

Baqui A H et al. (2004) conducted a community-based randomized controlled trial in Bangladesh to evaluate the effect of zinc therapy for the treatment of diarrhoea on the use of ORS, antibiotics and other drugs. Thirty clusters, each with about 200 children aged 3 to 59 months, were randomly allocated to intervention or comparison areas. There were 3,974 children in the intervention clusters and 4,096 children in the comparison clusters. Community health workers and community volunteers distributed packets of ORS and advised on feeding to parents who brought a child with diarrhoea in both study areas. In the intervention clusters, community health workers and community volunteers also distributed zinc syrup to children with diarrhoea and instructed the mothers on how to use the syrup. Children in the intervention areas received 20 mg zinc acetate per day for 14 days regardless of the duration of diarrhoeal episode, in a once daily dose of 5 ml. Trained field workers who were not involved in the implementation of the intervention made home visits every two months to collect data on diarrhoea morbidity, use of ORS and zinc therapy as well as other therapies for diarrhoea in the week before the interview. The study found that the use of ORS was significantly higher among children in the zinc intervention areas than those in the comparison areas (74.9% versus 50.2%, $P < 0.01$). The use of antibiotics in the zinc intervention areas was found to be significantly reduced compared to the comparison areas (odds ratio (OR) 0.30, 95% CI: 0.25, 0.35). The authors concluded that the significant reduction in antibiotic use and related behaviours in the intervention group demonstrated that the benefits of zinc supplementation extend well beyond reducing childhood morbidity and mortality. Zinc supplementation for diarrhoea in addition to ORS, could reduce inappropriate antibiotic use that is leading to antimicrobial-resistant pathogens.^{12 Level II-1}

5.2 SAFETY

With regards to safety, zinc salts has been approved as safe for consumption by United States Food and Drug Administration (USFDA).¹³

5.2.1 Vomiting

Lazzerini M et al. (2013) reported in their systematic review that eight trials involving 5,189 children found that vomiting was significantly more common in those given zinc supplementation across all age groups (RR 1.59, 95% CI 1.27, 1.99).^{10 Level I} One single trial found no difference in time to resolution of vomiting between zinc and placebo (13.63 ± 10.33 hours versus 16.35 ± 11.34 hours, $P = 0.1$).^{10 Level I} In the systematic review and meta-analysis by Lamberti L M et al. (2013), zinc-treated children had an increased risk of vomiting with RR 1.83, 95% CI: 1.40, 2.39.^{11 Level I}

5.2.2 Effect on copper levels

Lazzerini M et al. (2013) reported that no significant difference was found on copper levels between the zinc and placebo groups.^{10 Level I}

5.3 COST-EFFECTIVENESS

Mejia A et al. (2015) conducted a cost-effectiveness analysis of zinc supplementation for the treatment of acute diarrhoea in children younger than five years in Colombia. The cost-effectiveness analysis was performed from the perspective of the Colombian health system. The health options considered were the addition of zinc to the standard treatment for acute diarrhoea and the standard treatment without supplementation. The standard treatment for acute diarrhoea comprises continual feeding of the child during the episode and maintaining hydration with ORS. The recommended and used zinc dosage for treatment is 10 mg in children younger than six months and 20 mg in children older than six months for 10 to 14 days. The time horizon was one month. Effectiveness was extracted from a systematic review of literature. The specific data for Colombia were taken from local databases and observational studies. A typical case was constructed by reviewing guidelines and medical records and validated by experts to determine the costs. Costs were stated in Colombian pesos (COP) and US dollar (USD) for 2010. Deterministic sensitivity analysis was performed to evaluate the impact of changes in cost and effectiveness of the strategies on the results from the model. The analysis found that the results from the model indicated that zinc supplementation is a dominant strategy as it is less costly and more effective than standard treatment without zinc (reduction of \$15,210 COP (8.14 USD) per child). The results were sensitive to changes in the probability of hospitalization and of persistent diarrhoea. The authors concluded that zinc for the treatment of acute diarrhoea is a highly cost-effective strategy and is recommended for inclusion in the benefit plan of the Colombian health system. This intervention is more cost-effective in children with a higher risk of persistent diarrhoea and hospitalization.¹⁴

Gregorio G V et al. (2007) conducted a cost-effectiveness analysis among patients consulting the emergency room of a government institute in Philippines to determine whether zinc with ORS is more cost-effective than ORS alone in the treatment of acute diarrhoea. This cost-effectiveness analysis was conducted in 2003 using 117 of 138 patients included in the randomized controlled trial (RCT). Children between two and 59 months old with diarrhoea less than seven days duration and no evidence of dehydration were included in the study. Cost of treatment and outcome of participants of a randomized trial of zinc plus ORS versus ORS alone for acute diarrhoea were calculated. The direct medical, nonmedical and indirect costs were obtained using the societal perspective. Overall, the cost per patient was obtained by taking the sum of the direct medical and nonmedical costs and indirect cost. The mean total cost for each group was then obtained. The incremental cost-effectiveness ratio (ICER) was calculated. Sensitivity analysis was performed by altering the input values of the direct medical costs and indirect costs and by considering different durations of diarrhoea to assess the effects of uncertainties. The analysis found that there was significantly shorter duration of diarrhoea from time of consultation noted in the zinc group compared to the ORS group (mean \pm standard deviation (SD), 2.98 \pm 0.92 days versus 3.67 \pm 1.63, P = 0.009) with a difference of 0.69

days (16.6 hours). There were more patients in the zinc group with duration of diarrhoea less than four days from admission (92% versus 75%, $P = 0.780$) than the ORS group. The total cost of treatment was found to be less in the zinc group, with a cost difference of US\$ 1.6. The ICER showed that with use of zinc, the society saves \$2.4 per day of diarrhoea less than four days and spends \$0.03 per case of diarrhoea averted less than four days from consult. The bootstrap re-sampling was used to construct the cost-effectiveness plane. The bootstrap estimates of the cost and effect differences showed that most of estimates are in the quadrant where the zinc group is dominant, that is less costly and more effective. The authors concluded that the use of zinc with ORS reduced the total cost and duration of acute diarrhoea. The ICER suggests cost effectiveness of zinc supplementation but there is a need to further assess the role of zinc supplementation in a larger population.¹⁵

Robberstad B et al. (2004) conducted a cost-utility analysis aimed to analyse the incremental costs, effects and cost-effectiveness of zinc used as adjunct therapy to standard treatment of acute childhood diarrhoea, including dysentery, and to reassess the cost-effectiveness of standard case management with oral rehydration salt (ORS) among children less than five years old. A decision tree was used to model expected clinical outcomes and expected costs under four alternative treatment strategies; no treatment, standard case management (ORS), ORS plus zinc to non-dysenteric patients and ORS plus zinc as adjunct therapy to current standard treatment for all children with acute diarrhoea, including those with dysentery. The best available epidemiological, clinical and economic evidence was used in the calculations, and the United Republic of Tanzania was the reference setting. Probabilistic cost-effectiveness analysis was performed using a Monte-Carlo simulation technique and the potential impacts of uncertainty in single parameters were explored in one-way sensitivity analyses. Disability-adjusted life years (DALYs) were used as the outcome measure to simplify the comparison of cost-effectiveness across disease groups and settings. All monetary values were presented in 2001 US dollars (US\$) and costs and health consequences were discounted using a rate of 3% as baseline. The costs and consequences were all calculated using hypothetical diarrhoea cases as the denominator. Direct costs and effects were presented in societal perspective. The analysis found that zinc supplementation as an adjunct therapy to the standard management of diarrhoea for dysenteric, was found to be more cost effective (US\$ 73 per DALY) than ORS (US\$ 113 per DALY averted) and the results was particularly sensitive to mortality rates in non-dysenteric diarrhoea. The authors concluded that there is sufficient evidence to recommend the inclusion of zinc into standard case management of both dysenteric and non-dysenteric acute diarrhoea and that the findings are also applicable to other developing countries.¹⁶

In terms of price, the price for zinc supplementation in Malaysia was unknown due to limited availability. However the price for zinc supplementation in form of syrup in Indonesia is approximately RM 10.67 per 100 ml bottle and in form of diarrhoea kit which consisted of ORS as well as

10 of 20 mg tablets of zinc sulphate in Cambodia is approximately RM 1.60 per kit.

5.4 ORGANIZATIONAL ISSUES

5.4.1 Hospital stay

Lazzerini M et al. (2013) reported in their systematic review and meta-analysis that there was currently not enough evidence from well conducted randomized controlled trials to suggest that zinc supplementation during acute diarrhoea reduces hospitalisation.^{10 Level I} In the systematic review and meta-analysis by Lamberti L M et al. (2013), the duration of hospital stay among children hospitalised for diarrhoea was reduced by 37% (95% CI: 21%, 53%) comparing the zinc and control groups. From the outcomes pooled across studies conducted in China, Lamberti L M et al. (2013) found 32% (95% CI: 24.3%, 39.2%) reductions in the duration of hospitalisation among zinc-treated children with acute diarrhoea attributable to rotavirus and to non-specific causes.^{11 Level I}

5.4.2 Guidelines / Recommendations

UNICEF AND WHO

Global recommendations which were formulated by UNICEF and WHO in collaboration with the United States Agency for International Development (USAID) and experts worldwide, were issued in 2004 advocating oral zinc supplementation in addition to ORS in the management of diarrhoea.¹⁷

These new recommendations stated that health care workers should:

- counsel mothers to begin administering suitable available home fluids immediately upon onset of diarrhoea in a child
- treat dehydration with ORS solution (or with an intravenous electrolyte solution in cases of severe dehydration)
- emphasize continued feeding or increased breastfeeding during, and increased feeding after the diarrhoeal episode
- use antibiotics only when appropriate, i.e. in the presence of bloody diarrhoea or shigellosis, and abstain from administering anti-diarrhoeal drugs
- provide children with 20 mg per day of zinc supplementation for 10–14 days (10 mg per day for infants under six months old)
- advise mothers of the need to increase fluids and continue feeding during future episodes

The zinc salt used to prepare syrups or tablets for use in the management of diarrhoea should be water soluble. Therefore, the zinc salts that should be used are zinc sulphate, zinc acetate and zinc gluconate.¹⁷

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and European Society for Pediatric Infectious Diseases (ESPID)

In updated Evidence-Based Guidelines for the Management of Acute Gastroenteritis in Children in Europe in 2014, it is stated that children age more than six months in developing countries may benefit from the use of zinc in the treatment of acute gastroenteritis. However, in the regions where zinc deficiency is rare, no benefit from the use of zinc is expected.¹⁸

5.5 LIMITATIONS

This technology review has several limitations. The selection of studies was done by one reviewer. Although there was no restriction in language during the search but only English full text articles were included in this report.

6. CONCLUSION

6.1 Effectiveness

There was good level of retrievable evidence to suggest that zinc supplementation was able to shorten the duration of acute diarrhoea as well as reduce the stool output and stool frequency among children younger than five years old with acute diarrhoea. The effect appears greater in children with signs of moderate malnutrition. However, the evidence with regards to the benefit of zinc supplementation for children less than six months of age was unclear. Limited good level of retrievable evidence to suggest that zinc supplementation was associated with increased use of ORS and decreased use of antibiotics during acute diarrhoea. There was insufficient evidence to suggest that zinc supplementation during acute diarrhoea reduces mortality.

6.2 Safety

Good level of retrievable evidence to suggest that the use of zinc supplementation in the management of diarrhoea for children younger than five years old was safe. Most common complication reported was vomiting. However, the evidence found no difference in time to resolution of vomiting between zinc and placebo.

6.3 Cost-effectiveness

Based on the two cost-effectiveness analyses and one cost-utility analysis, zinc supplementation as an adjunct in the management of diarrhoea in children younger than five years old was found to be more cost-effective than standard treatment.

6.4 Organizational issues

- **Hospital stay**

There was good level of retrievable evidence to suggest that zinc supplementation during acute diarrhoea was associated with reduction

in the duration of hospital stay among children hospitalised for diarrhoea compared to the control groups.

- **Guidelines**

WHO and UNICEF have issued a global recommendation in 2004 which advised zinc supplementation in addition to ORS for the treatment of all diarrhoea episodes among children younger than five years of age. ESPGHAN and ESPID stated that children age more than six months in developing countries may benefit from the use of zinc in the treatment of acute gastroenteritis. However, in the regions where zinc deficiency is rare, no benefit from the use of zinc is expected.

8. REFERENCES

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11. Lamberti LM, Walker CL, Chan KY et al. Oral zinc supplementation for the treatment of acute diarrhea in children: a systematic review and meta-analysis. *Nutrients.* 2013;5(11):4715-4740.
12. Baqui AH, Black RE, El Arifeen S et al. Zinc therapy for diarrhoea increased the use of oral rehydration therapy and reduced the use of antibiotics in Bangladeshi children. *J Health Popul Nutr.* 2004;22(4):440-442.
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9. APPENDIX

9.1. Appendix 1: LITERATURE SEARCH STRATEGY

| |
|--|
| Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1946 to present |
|--|

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

-
- 1 Diarrhea/
 - 2 diarrhea*.tw.
 - 3 diarrhoea*.tw.
 - 4 Diarrhea, Infantile/
 - 5 (infantile adj1 (diarrhea* or diarrhoea*)).tw.
 - 6 Childhood diarrh*.tw.
 - 7 childhood diarrhoea.tw.
 - 8 1 or 2 or 3 or 4 or 5 or 6 or 7
 - 9 Zinc/
 - 10 Zinc supplementation.tw.
 - 11 Zinc supplement.tw.
 - 12 zinc gluconate.tw.
 - 13 Zinc Sulfate/
 - 14 (zinc adj1 sulfate).tw.
 - 15 Zinc Acetate/
 - 16 (zinc adj1 acetate).tw.
 - 17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
 - 18 8 and 17

| OTHER DATABASES | |
|---|---|
| EBM Reviews - Cochrane Central Register of Controlled Trials | } |
| EBM Reviews - Database of Abstracts of Review of Effects | |
| EBM Reviews - Cochrane database of systematic reviews | } Same MeSH, keywords, limits used as per MEDLINE search |
| EBM Reviews - Health Technology Assessment | |
| EBM Reviews- NHS economic evaluation database | } |
| INAHTA | |

PubMed

(((((((((Diarrhea/[MeSH Terms]) OR diarrhea*[Title/Abstract]) OR diarrhoea*[Title/Abstract]) OR Diarrhea, Infantile/[MeSH Terms]) OR ((infantile adj1 (diarrhea*[Title/Abstract] OR diarrhoea*)) [Title/Abstract])) OR Childhood diarrh*[Title/Abstract]) OR childhood diarrhoea[Title/Abstract])) AND (((zinc/[MeSH Terms]) OR zinc supplementation[Title/Abstract]) OR zinc supplement[Title/Abstract]))

9.2. Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

***SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE
(Harris 2001)***

9.3. Appendix 3

Evidence Table : Efficacy / Effectiveness

Question : Is zinc supplement effective as adjuvant therapy in management of diarrhoea in children?

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|--|---|----|---|---------------------------|------------|-------------------------------------|--|------------------|
| 1. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev. 2013 Jan 31;1:CD005436. | <p>Sytematic review and meta-analysis</p> <p>Aim: To evaluate oral zinc supplementation for treating children with acute or persistent diarrhoea.</p> <p>Method: Systematic search was performed in Cochrane Infectious Diseases Group Specialized Register, CENTRAL (<i>The Cochrane Library</i> 2011, Issue 11), MEDLINE, EMBASE, LILACS, CINAHL, <i>m</i>RCT, and reference lists, for randomized controlled trials comparing oral zinc supplementation with placebo in children aged one month to five years with acute or persistent diarrhoea, including dysentery.</p> | I | Twenty-four trials, enrolling 9128 children were included in the review | Oral zinc supplementation | Placebo | | <p>Results: <u>Acute diarrhoea</u> -Diarrhoea duration was reduced in children given zinc by about 12 hours (mean difference (MD) -12.63, 95% CI: -21.05 to 4.21 hours, 4446 children, 15 trials) but there was significant heterogeneity between trials</p> <p>-The pooled point estimate suggests a benefit with zinc for children > six months although this was not statistically significant and moderate heterogeneity remained (MD -10.44.h, 95% CI -21.13 to 0.25 hours; 2175 children, six trials)</p> <p><u>Diarrhoea on days three, five, and seven</u> -Zinc supplementation resulted in fewer children continuing to have diarrhoea at day three: (RR 0.77, 95% CI 0.67 to 0.89; 1568 children, three trials), at day five: (RR 0.67, 95% CI 0.51 to 0.89;1730 children, five trials), and at day seven: (RR 0.82, 95% CI 0.72 to 0.94; 5528 children, 10 trials)</p> | Cochrane review |

Evidence Table : **Efficacy / Effectiveness**
Question : **Is zinc supplement effective as adjuvant therapy in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|---|---|----|--|--------------|------------|-------------------------------------|--|------------------|
| <p>1. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev. 2013 Jan 31;1:CD005436.</p> | <p>Both authors assessed trial eligibility and risk of bias, extracted and analysed data, and drafted the review.</p> <p>Diarrhoea duration and severity were the primary outcomes.</p> <p>Outcomes were summarized using risk ratios (RR) and continuous outcomes using mean differences (MD) with 95% confidence intervals (CI).</p> <p>Meta-analyses (using the fixed or random-effects model) was done and heterogeneity was assessed.</p> <p>The quality of evidence has been assessed using the GRADE methods</p> | | | | | | <p>For diarrhoea at day seven, heterogeneity was markedly reduced when the results stratified by age: No benefit of zinc was detected in children under six months While zinc had a benefit in children older than six months (RR 0.73, 95% CI 0.61 to 0.8; 3865 children, six trials) and in trials recruiting both age groups (RR 0.31, 95% CI 0.18 to 0.52; 589 children, three trials)</p> <p>Hospitalization</p> <p>One hospital trial showed a significant reduction in the duration of hospitalization in children treated with zinc compared to those given placebo (MD 4.33 days ± 1.38 vs 5.81 ± 2.08 days).</p> <p>Of the two community trials reporting on hospitalization, one found no difference between groups and the second reported no hospitalizations in the zinc group and only one in the placebo group.</p> | |

Evidence Table : Efficacy/Effectiveness
 Question : Is zinc supplement effective as adjuvant therapy in management of diarrhoea in children?

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|--|----------------------|----|--|--------------|------------|-------------------------------------|---|------------------|
| 1. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev. 2013 Jan 31;1:CD005436. doi: 10.1002/14651858. CD005436 | | | | | | | <p>In children with persistent diarrhoea All trials of persistent diarrhoea enrolled children aged over six months.</p> <p>Diarrhoea duration Zinc supplementation reduced the duration of persistent diarrhoea (MD -15.83 hours, 95%-25.43 to -6.24 hours; 529 children, five trials), with no evidence of heterogeneity.</p> <p>Diarrhoea on days three, five, and seven There was no evidence of a benefit with zinc in the one trial that reported on diarrhoea at days three and five and two trials that reported on diarrhoea at day seven</p> | |

Evidence Table : **Efficacy/Effectiveness**
Question : **Is zinc supplement effective as adjuvant therapy in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|---|----------------------|----|--|--------------|------------|-------------------------------------|---|------------------|
| 1. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev. 2013 Jan 31;1:CD005436. doi: 10.1002/14651858.CD005436 | | | | | | | <p>Conclusion:</p> <p>In areas where the prevalence of zinc deficiency or the prevalence of moderate malnutrition is high, zinc may be of benefit in children aged six months or more.</p> <p>The current evidence does not support the use of zinc supplementation in children below six months of age.</p> | |

Evidence Table : **Efficacy/effectiveness**
Question : **Is zinc supplement effective as adjuvant therapy in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|--|---|----|--|---------------------------------------|--------------------|-------------------------------------|---|------------------|
| 2. Lamberti LM, Walker CL, Chan KY et al. Oral zinc supplementation for the treatment of acute diarrhea in children: a systematic review and meta-analysis. <i>Nutrients</i> . 2013;5(11):4715-4740. | <p>Systematic review and meta-analysis</p> <p>Aim: To estimate the effect of oral therapeutic zinc supplementation on selected morbidity and mortality outcomes among children under five years of age.</p> <p>Method: Systematic literature search for studies published in any language between 1980 and November 2012, in the following databases: Biosis, Cumulative Index to Nursing and Allied Health (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL), Embase, the WHO International Clinical Trials Registry Platform (ICTRP), Global Health, Latin American and Caribbean Health Sciences Literature (LILACS), PubMed,</p> | I | 89 Chinese and 15 non-Chinese studies for the review with a total of 18,822 diarrhoea cases (9469 zinc and 9353 control) | Oral therapeutic zinc supplementation | Supportive therapy | | <p>Results: <u>Outcomes pooled across studies outside China</u></p> <p>-Acute episodes were 4% (95% CI: 1%–8%) shorter in duration among children treated with zinc compared to those receiving placebo -Among children hospitalized for diarrhoea, the duration of hospitalization was reduced by 37% (95% CI: 21%–53%) comparing the zinc and control groups -Stool frequency was decreased by 6% (95% CI: 2%–10%) among zinc-treated children -Zinc-treated children had a reduced relative risk (RR) of acute diarrhoea lasting beyond three and seven days and an increased risk of vomiting (RR: 1.83; 95% CI: 1.40–2.39)</p> <p><u>Outcomes pooled across studies conducted in China</u></p> <p>-Reductions in the duration of diarrhoea, hospitalization, fever, vomiting, stool output and stool frequency among zinc-treated children with acute diarrhoea attributable to rotavirus and to non-specific causes</p> | |

Evidence Table : **Efficacy / Effectiveness**
Question : **Is zinc supplement effective as adjuvant therapy in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|---|---|----|--|--------------|------------|-------------------------------------|--|------------------|
| <p>2. Lamberti LM, Walker CL, Chan KY, Jian WY, Black RE. Oral zinc supplementation for the treatment of acute diarrhea in children: a systematic review and meta-analysis. <i>Nutrients</i>. 2013;5(11):4715-4740.</p> | <p>Scopus, Web of Science, IndMed, Egyptian Universities Library Consortium, Index Medicus for the Eastern Mediterranean Region (IMEMR), China National Knowledge Infrastructure (CNKI), WanFang, and Chinese BioMedical (CBM) database</p> <p>Inclusion of studies was restricted to individually randomized controlled trials (RCTs) of children under five years of age with acute diarrhoea, including dysentery, where diarrhoea was defined as the passage of at least three loose or watery stools in a 24-h period.</p> <p>Included studies were reviewed for the following outcomes: diarrhoea duration; the proportion of diarrhoea episodes lasting >3 and >7 days; duration of hospitalization</p> | | | | | | <p>-The reduction in the duration of diarrhoea was 37% (95% CI: 35%–39%) among non-specific episodes and 31% (95% CI: 29%–34%) among rotavirus episodes -The RR of diarrhoea lasting beyond three days was reduced among zinc-treated patients with non-specific (RR: 0.73; 95% CI: 0.66–0.79) and rotavirus (RR: 0.70; 95% CI: 0.63–0.78) diarrhoea</p> <p>Conclusion:</p> <p>Studies conducted in and outside China report reductions in morbidity as a result of oral therapeutic zinc supplementation for acute diarrhoea among children under five years of age. The WHO recommendation for zinc treatment of diarrhoea episodes should be supported in all low-middle- income countries.</p> | |

Evidence Table : **Efficacy / Effectiveness**
Question : **Is zinc supplement effective as adjuvant therapy in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|---|--|----|--|--------------|------------|-------------------------------------|-------------------------------|------------------|
| <p>2. Lamberti LM, Walker CL, Chan KY, Jian WY, Black RE. Oral zinc supplementation for the treatment of acute diarrhea in children: a systematic review and meta-analysis. <i>Nutrients</i>. 2013;5(11):4715-4740.</p> | <p>duration of fever; duration of vomiting; proportion of cases vomiting; stool frequency (number per day); stool output (mL); and death from diarrhoea or any cause.</p> <p>Two independent reviewers entered data into structured tables, and discrepancies were resolved in consultation with a third reviewer.</p> <p>STATA 12.0 was used to pool select outcomes and to generate estimates of percentage difference and relative risk comparing outcomes between zinc and control groups.</p> | | | | | | | |

Evidence Table : **Efficacy/effectiveness**
Question : **Is zinc supplement effective as adjuvant therapy in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|---|--|-------------|---|--|-------------------------------|-------------------------------------|---|------------------|
| <p>3. Baqui AH, Black RE, El Arifeen S et al. Zinc therapy for diarrhoea increased the use of oral rehydration therapy and reduced the use of antibiotics in Bangladeshi children. J Health Popul Nutr. 2004 Dec;22(4):440-442.</p> | <p>Community based randomized controlled trial</p> <p>Aim: to evaluate the effect of zinc therapy for the treatment of diarrhoea on the use of ORS, antibiotics and other drugs</p> <p>Method: Thirty clusters, each with about 200 children aged 3 to 59 months, were randomly allocated to intervention or comparison areas.</p> <p>Community health workers and community volunteers distributed packets of ORS and advised on feeding to parents who brought a child with diarrhoea in both study areas.</p> | <p>II-1</p> | <p>3,974 children in the intervention clusters and 4,096 children in the comparison clusters.</p> | <p>Oral therapeutic zinc supplementation + ORS + continual feeding</p> | <p>ORS+ continual feeding</p> | | <p>Results:</p> <p>The use of ORS was significantly higher among children in the zinc intervention areas than those in the comparison areas (74.9% versus 50.2%, P < 0.01).</p> <p>The use of antibiotics in the zinc intervention areas was found to be significantly reduced compared to the comparison areas (odds ratio (OR) 0.30, 95% CI: 0.25, 0.35).</p> <p>Authors conclusion:</p> <p>The significant reduction in antibiotic use and related behaviours in the intervention group demonstrated that the benefits of zinc supplementation extend well beyond reducing childhood morbidity and mortality. Zinc supplementation for diarrhoea in addition to ORS, could reduce inappropriate antibiotic use that is leading to antimicrobial-resistant pathogens</p> | |

Evidence Table : **Efficacy/effectiveness**
Question : **Is zinc supplement effective as adjuvant therapy in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|---|--|----|--|--------------|------------|-------------------------------------|-------------------------------|------------------|
| <p>3. Baqui AH, Black RE, El Arifeen S et al. Zinc therapy for diarrhoea increased the use of oral rehydration therapy and reduced the use of antibiotics in Bangladeshi children. J Health Popul Nutr. 2004 Dec;22(4):440-442.</p> | <p>In the intervention clusters, community health workers and community volunteers also distributed zinc syrup to children with diarrhoea and instructed the mothers on how to use the syrup.</p> <p>Children in the intervention areas received 20 mg zinc acetate per day for 14 days regardless of the duration of diarrhoeal episode, in a once daily dose of 5ml.</p> <p>Trained field workers who were not involved in the implementation of the intervention made home visits every two months to collect data on diarrhoea morbidity, use of ORS and zinc therapy as well as other therapies for diarrhoea in the week before the interview.</p> | | | | | | | |

Evidence Table : **Safety**
Question : **Is zinc supplement safe as adjuvant therapy in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|--|--|----|---|---------------------------|------------|-------------------------------------|---|------------------|
| 1. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev. 2013 Jan 31;1:CD005436. | <p>Sytematic review and meta-analysis</p> <p>Aim: To evaluate oral zinc supplementation for treating children with acute or persistent diarrhoea.</p> <p>Method: Systematic search was performed in Cochrane Infectious Diseases Group Specialized Register, CENTRAL (<i>The Cochrane Library</i> 2011, Issue 11), MEDLINE, EMBASE, LILACS, CINAHL, mRCT, and reference lists, for randomized controlled trials comparing oral zinc supplementation with placebo in children aged one month to five years with acute or persistent diarrhoea, including dysentery.</p> | I | Twenty-four trials, enrolling 9128 children were included in the review | Oral zinc supplementation | Placebo | | <p>Results: Adverse events Eight trials reported vomiting, which was significantly more common in those given zinc across all age groups (RR 1.59, 95% CI 1.27 to 1.99) There was significant heterogeneity among trials (P = 0.001, I² = 69.3%), and differences in control event rates.</p> <p>One single trial on gastroenteritis due to rotavirus found no difference in time to resolution of vomiting between zinc and placebo (13.63 ± 10.33 hours vs 16.35 ± 11.34 hours, P = 0.1; Dalgic 2011)</p> <p>Three trials reported on copper levels, with no significant differences between the zinc and placebo groups.</p> <p>Two studies reported the mean change in serum copper on the last day of supplementation (seven and 14 days after recovery): -1.1 ± 5.5 µmol/dL in the zinc group versus -1.5 ± 4.2 µmol/dL in the placebo group in one trial (Strand 2002), and -41.2 ± 418.8 µg/dL in the zinc group versus -79.4 ± 429.2 µg/dL in the placebo group in the second trial (Patel 2009).</p> | Cochrane review |

Evidence Table : **Safety**
Question : **Is zinc supplement safe as adjuvant therapy in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|---|---|----|--|--------------|------------|-------------------------------------|--|------------------|
| <p>1. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev. 2013 Jan 31;1:CD005436.</p> | <p>Both authors assessed trial eligibility and risk of bias, extracted and analysed data, and drafted the review.</p> <p>Diarrhoea duration and severity were the primary outcomes.</p> <p>Outcomes were summarized using risk ratios (RR) and continuous outcomes using mean differences (MD) with 95% confidence intervals (CI).</p> <p>Meta-analyses (using the fixed or random-effects model) was done and heterogeneity was assessed.</p> <p>The quality of evidence has been assessed using the GRADE methods</p> | | | | | | <p>Mean serum copper after 14 days was 121 mg/L in zinc group versus 127 mg/L in the control in one trial (Bhatnagar 2004a),</p> | |

Evidence Table : **Safety**
Question : **Is zinc supplement safe as adjuvant therapy in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|--|---|----|--|---------------------------------------|--------------------|-------------------------------------|--|------------------|
| <p>2. Lamberti LM, Walker CL, Chan KY et al. Oral zinc supplementation for the treatment of acute diarrhea in children: a systematic review and meta-analysis. <i>Nutrients</i>. 2013;5(11):4715-4740.</p> | <p>Systematic review and meta-analysis</p> <p>Aim: To estimate the effect of oral therapeutic zinc supplementation on selected morbidity and mortality outcomes among children under five years of age.</p> <p>Method: Systematic literature search for studies published in any language between 1980 and November 2012, in the following databases: Biosis, Cumulative Index to Nursing and Allied Health (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL), Embase, the WHO International Clinical Trials Registry Platform (ICTRP), Global Health, Latin American and Caribbean Health Sciences Literature (LILACS), PubMed,</p> | I | 89 Chinese and 15 non-Chinese studies for the review with a total of 18,822 diarrhoea cases (9469 zinc and 9353 control) | Oral therapeutic zinc supplementation | Supportive therapy | | <p>Results:</p> <p>Zinc-treated children had an increased risk of vomiting (RR: 1.83; 95% CI: 1.40–2.39)</p> | |

Evidence Table : **Safety**
Question : **Is zinc supplement safe as adjuvant therapy in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|---|---|----|--|--------------|------------|-------------------------------------|-------------------------------|------------------|
| <p>2. Lamberti LM, Walker CL, Chan KY, Jian WY, Black RE. Oral zinc supplementation for the treatment of acute diarrhea in children: a systematic review and meta-analysis. <i>Nutrients</i>. 2013;5(11):4715-4740.</p> | <p>Scopus, Web of Science, IndMed, Egyptian Universities Library Consortium, Index Medicus for the Eastern Mediterranean Region (IMEMR), China National Knowledge Infrastructure (CNKI), WanFang, and Chinese BioMedical (CBM) database</p> <p>Inclusion of studies was restricted to individually randomized controlled trials (RCTs) of children under five years of age with acute diarrhoea, including dysentery, where diarrhoea was defined as the passage of at least three loose or watery stools in a 24-h period.</p> <p>Included studies were reviewed for the following outcomes: diarrhoea duration; the proportion of diarrhoea episodes lasting >3 and >7 days; duration of hospitalization</p> | | | | | | | |

Evidence Table : **Safety**
Question : **Is zinc supplement safe as adjuvant therapy in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|---|--|----|--|--------------|------------|-------------------------------------|-------------------------------|------------------|
| <p>2. Lamberti LM, Walker CL, Chan KY, Jian WY, Black RE. Oral zinc supplementation for the treatment of acute diarrhea in children: a systematic review and meta-analysis. <i>Nutrients</i>. 2013;5(11):4715-4740.</p> | <p>duration of fever; duration of vomiting; proportion of cases vomiting; stool frequency (number per day); stool output (mL); and death from diarrhoea or any cause.</p> <p>Two independent reviewers entered data into structured tables, and discrepancies were resolved in consultation with a third reviewer.</p> <p>STATA 12.0 was used to pool select outcomes and to generate estimates of percentage difference and relative risk comparing outcomes between zinc and control groups.</p> | | | | | | | |

Evidence Table : **Cost-effectiveness**
Question : **Is zinc supplementation is cost-effective in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|--|---|----|--|--|--|-------------------------------------|--|------------------|
| <p>1. Mejía A, Atehortúa S, Flórez ID et al. Cost-effectiveness analysis of zinc supplementation for treatment of acute diarrhea in children younger than 5 years in Colombia. J Pediatr Gastroenterol Nutr. 2015;60(4):515-520.</p> | <p>Cost-effectiveness analysis</p> <p>Aim: To determine the cost-effectiveness of zinc supplementation for the treatment of acute diarrhea (AD) in children younger than 5 years in Colombia</p> <p>Methods: The cost-effectiveness analysis was performed from the perspective of the Colombian health system</p> <p>The health options considered were the following: the addition of zinc to the standard treatment for AD and the standard treatment without supplementation. The standard treatment for AD comprises Plan A recommended by WHO, which includes continual feeding of the child during the episode and maintaining hydration with ORS.</p> | I | | Zinc supplementation plus standard treatment | Standard treatment for acute diarrhoea: -continual feeding -maintaining hydration with ORS | | <p>Results: The results from the model indicate that zinc supplementation is a dominant strategy; it is less costly and more effective than standard.</p> <p>The average cost of an episode of diarrhoea in Colombia is \$79,432 COP (42.5 USD), and an episode of a child receiving zinc would decrease it to \$64,222 COP (34.36 USD), a reduction of \$15,210 COP (8.14 USD). The zinc strategy is more effective (lower mortality associated with diarrhoea) and of a lower cost.</p> <p>The results are sensitive to changes in the probability of hospitalization and of persistent diarrhoea.</p> <p>Conclusion: Zinc for the treatment of AD is a highly cost-effective strategy and is recommended for inclusion in the benefit plan of the Colombian health system. This intervention is more cost-effective in children with a higher risk of persistent diarrhoea and hospitalization.</p> | |

Evidence Table : **Cost-effectiveness**
Question : **Is zinc supplementation is cost-effective in management of diarrhoea in children?**

| Bibliographic citation | Study Type / Methods | LE | Number of patients and patient characteristics | Intervention | Comparison | Length of follow up (if applicable) | Outcome measures/ Effect size | General comments |
|---|---|----|--|--------------|------------|-------------------------------------|-------------------------------|------------------|
| <p>1. Mejía A, Atehortúa S, Flórez ID et al. Cost-effectiveness analysis of zinc supplementation for treatment of acute diarrhea in children younger than 5 years in Colombia. J Pediatr Gastroenterol Nutr.2015;60(4):515-520.</p> | <p>The recommended and used zinc dosage for treatment is 10 mg in children younger than 6 months and 20 mg in children older than 6 months for 10 to 14 days.</p> <p>To estimate the expected costs and health outcomes of the 2 alternatives, a decision model that reflects the health outcomes of patients with AD who are younger than 5 year was constructed.</p> <p>The analysis only considers children from birth until they are 5 years old, and children with AD and an underlying chronic disease (severe malnutrition and immunosuppression) were excluded.</p> | | | | | | | |

Evidence Table : **Cost-effectiveness**
Question : **Is zinc supplementation is cost-effective in management of diarrhoea in children?**

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| <p>1. Mejía A, Atehortúa S, Flórez ID et al. Cost-effectiveness analysis of zinc supplementation for treatment of acute diarrhea in children younger than 5 years in Colombia. J Pediatr Gastroenterol Nutr.2015;60(4):515-520.</p> | <p>The time horizon was one month.</p> <p>Effectiveness was extracted from a systematic review of literature.</p> <p>The specific data for Colombia were taken from local databases and observational studies.</p> <p>To determine the costs, a typical case was constructed by reviewing guidelines and medical records and validated by experts.</p> <p>To evaluate the resources consumed, Colombian tariff manuals were used.</p> <p>Costs were stated in Colombian pesos (COP) and US dollar (USD) for 2010.</p> | | | | | | | |

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| <p>1. Mejía A, Atehortúa S, Flórez ID et al. Cost-effectiveness analysis of zinc supplementation for treatment of acute diarrhea in children younger than 5 years in Colombia. J Pediatr Gastroenterol Nutr. 2015;60(4):515-520.</p> | <p>Deterministic sensitivity analysis was performed to evaluate the impact of changes in cost and effectiveness of the strategies on the results from the model</p> | | | | | | | |

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| <p>2.Robberstad B, Strand T, Black RE, Sommerfelt H. Cost-effectiveness of zinc as adjunct therapy for acute childhood diarrhoea in developing countries. Bull World Health Organ. 2004 Jul;82(7):523-31</p> | <p>Cost-effectiveness analysis Aim: To analyse the incremental costs, effects and cost-effectiveness of zinc used as adjunct therapy to standard treatment of acute childhood diarrhoea, including dysentery, and to reassess the cost-effectiveness of standard case management with oral rehydration salt (ORS). Method: A generalized incremental cost-effectiveness analysis was performed using DALYs as the outcome measure to simplify the comparison of cost-effectiveness across disease groups and settings. In the calculation of DALYs, we used a Tanzanian life table with a life expectancy of 46.5 years at birth</p> | | | <p>Zinc supplementation plus standard management with ORS</p> | <p>ORS</p> | | <p>Results:</p> <p>The reassessed mean CER for ORS (I) was US\$ 113 per DALY averted, or about US\$ 3200 per child death averted</p> <p>The mean incremental CER of adding zinc to the treatment of patients without dysentery was US\$ 40 per DALY averted and approximately US\$ 1200 per death averted</p> <p>Expanding the programme to cover not only the non-dysenteric but also dysenteric cases of acute diarrhoea yielded mean incremental CERs of US\$ 11 per DALY and US\$ 307 per death averted</p> <p>The average mean CERs of providing ORS and zinc to all children with acute diarrhoea was US\$ 73 per DALY and about US\$ 2100 per death averted</p> | |

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| <p>2.Robberstad B, Strand T, Black RE, Sommerfelt H. Cost-effectiveness of zinc as adjunct therapy for acute childhood diarrhoea in developing countries. Bull World Health Organ. 2004 Jul;82(7):523-31</p> | <p>The costs per child death averted were also calculated. All monetary values are presented in 2001 US dollars (US\$) and costs and health consequences are discounted using a rate of 3% as baseline</p> <p>The costs and consequences were all calculated using hypothetical diarrhoea cases as the denominator</p> <p>direct costs and effects in a societal perspective, meaning that costs to the health system and some patient costs were included</p> <p>Monte-Carlo simulation approach was used to account for simultaneous uncertainties in both cost and effect measures. Incremental and average costs, effects and cost-effectiveness were calculated for each of the alternative treatment protocols</p> | | | | | | <p>ORS was found to be less cost-effective than previously thought. The use of zinc as adjunct therapy significantly improved the cost-effectiveness of standard management of diarrhoea for dysenteric as well as non-dysenteric illness.</p> <p>The results were particularly sensitive to mortality rates in non-dysenteric diarrhoea, but the alternative interventions can be defined as highly cost-effective even in pessimistic scenarios.</p> <p>Conclusion: There is sufficient evidence to recommend the inclusion of zinc into standard case management of both dysenteric and non-dysenteric acute diarrhoea.</p> | |

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| 2.Robberstad B, Strand T, Black RE, Sommerfelt H. Cost-effectiveness of zinc as adjunct therapy for acute childhood diarrhoea in developing countries. Bull World Health Organ. 2004 Jul;82(7):523-31 | Finally, a one-way sensitivity analysis was performed for key variables | | | | | | | |

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| <p>3. Gregorio GV, Dans LF, Cordero CP, Panelo CA. Zinc supplementation reduced cost and duration of acute diarrhea in children. J Clin Epidemiol. 2007 Jun;60(6):560-566.</p> | <p>Randomized controlled trial and cost-effectiveness analysis</p> <p>Aim: To determine whether zinc with oral rehydration solution (ORS) is more cost effective than ORS alone in the treatment of acute diarrhoea</p> <p>Method: This cost effectiveness analysis (CEA) was conducted in 2003 using 117 of 138 patients included in the randomized controlled trial (RCT).</p> <p>Patients were recruited at the Emergency Room (ER) of the institution and from two satellite centres (San Andres and Paco local health units) within 5 km from study site. Those recruited in the satellite centres were sent to the ER and if necessary, hydration and all laboratory work-ups were done there.</p> | | | Zinc supplementation | ORS alone | | <p>Results: Clinical outcomes There was significantly shorter duration of diarrhoea from time of consultation noted in the zinc group compared to the ORS group (mean \pm standard deviation (SD), 2.98 \pm 0.92 days versus 3.67 \pm 1.63, P = 0.009) with a difference of 0.69 days (16.6 hours)</p> <p>There were more patients in the zinc group with duration of diarrhoea less than four days from admission (92% versus 75%, P = 0.780) than the ORS group.</p> <p>The total cost of treatment was found to be less in the zinc group, with a cost difference of US\$ 1.6. The ICER showed that with use of zinc, the society saves \$2.4 per day of diarrhoea less than four days and spends \$0.03 per case of diarrhoea averted less than four days from consult.</p> <p>The bootstrap re-sampling was used to construct the cost-effectiveness plane.</p> | |

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| <p>3. Gregorio GV, Dans LF, Cordero CP, Pabelo CA. Zinc supplementation reduced cost and duration of acute diarrhea in children. J Clin Epidemiol. 2007 Jun;60(6):560-566.</p> | <p>Children between 2 and 59 months old with diarrhea 7 days duration and no evidence of dehydration were included.</p> <p>After informed consent, baseline features were taken.</p> <p>The subjects were then randomized by block randomization with use of sealed envelopes containing the treatment assignment for each day.</p> <p>The day of randomization was considered day 0 of the study.</p> <p>The study group received 20 mg zinc sulfate tablet per day for 14 days along with standard WHO-ORS. The control group received WHO-ORS only.</p> <p>The zinc tablets, taken 2 hours after food intake, were dissolved in water or milk before administration or were taken as is by older children.</p> | | | | | | <p>The bootstrap estimates of the cost and effect differences showed that most of estimates are in the quadrant where the zinc group is dominant, that is less costly and more effective.</p> <p>Conclusion:</p> <p>The authors concluded that the use of zinc with ORS reduced the total cost and duration of acute diarrhoea.</p> <p>The ICER suggests cost effectiveness of zinc supplementation but there is a need to further assess the role of zinc supplementation in a larger population</p> | |

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| <p>3. Gregorio GV, Dans LF, Cordero CP, Panelo CA. Zinc supplementation reduced cost and duration of acute diarrhea in children. J Clin Epidemiol. 2007 Jun;60(6):560-566.</p> | <p>The WHO-ORS was provided in sachet to be dissolved in a litre of clean water and consumed in 24 hours.</p> <p>During follow-up visits between days 3e5 and 14e17, the presence or absence of diarrhoea was ascertained through interview of caregivers. The exact day on which the stools returned to normal frequency and consistency was asked.</p> <p>The duration of diarrhoea was computed from the day of consultation up to the time the bowel movement has returned to its normal frequency and consistency followed by a 24-hour diarrhoea free period.</p> | | | | | | | |

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| <p>3. Gregorio GV, Dans LF, Cordero CP, Pabello CA. Zinc supplementation reduced cost and duration of acute diarrhea in children. J Clin Epidemiol. 2007 Jun;60(6):560-566.</p> | <p>The study personnel inspected the blister pack of zinc and counted the number of tablets left. Mothers were also asked if they have given the zinc tablets to anyone aside from the patient.</p> <p>A patient was considered cured if there is cessation of diarrhea within 10 days after consult. Treatment failure was defined as the presence of any adverse drug reactions to zinc or if the duration of diarrhea was >10 days from consultation.</p> <p>A patient was withdrawn if he develops other medical conditions requiring antibiotic therapy or noncompliance with intake of zinc (<80% intake of recommended dose).</p> | | | | | | | |

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| 3. Gregorio GV, Dans LF, Cordero CP, Pabelo CA. Zinc supplementation reduced cost and duration of acute diarrhea in children. J Clin Epidemiol. 2007 Jun;60(6):560-566. | <p>The direct medical, nonmedical and indirect costs were obtained, using the societal perspective.</p> <p>The incremental cost-effectiveness ratio (ICER) was calculated.</p> | | | | | | | |