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Evidence for the Safety and Efficacy of Zinc Supplementation in the Management of Diarrhoea

A document prepared by the Department of Child and Adolescent Health and Development of the World Health Organization (WHO) and by the Supply Division of the United Nations Children's Fund (UNICEF)

Following the publication in 2004 of the WHO/UNICEF joint statement on the clinical management of acute diarrhoea (*1*), recommending the use of zinc in the clinical management of acute diarrhoea, efforts to ensure the availability and use of suitable zinc products in countries were conducted by WHO, UNICEF, USAID and Johns Hopkins University. In 2005, a collaborative effort with the United States Pharmacopoeia (USP) helped establish monographs and reference standards for tablets and oral solutions, and led to the development of a document entitled *Production of zinc tablets and zinc oral solutions: guidelines for programme managers and pharmaceutical manufacturers* (*2*). In addition, evidence on the efficacy and safety of zinc in the management of acute diarrhoea was collated and presented to the WHO Expert Committee on the Use of Essential Medicines in March 2005 to support the inclusion of zinc in the 14th revised edition of the WHO Model List of Essential Medicines in March 2005 (*3*). At the same time, UNICEF Supply Division identified international suppliers of zinc products that met the established quality criteria of the USP monograph and fulfilled the WHO criteria of good manufacturing practice. In May 2006, an international competitive tender was issued, to which seven zinc product manufacturers from four countries responded. Following thorough technical evaluation, including laboratory analysis of samples at the USP Laboratories in Washington, DC, one supplier based in France (Nutriset), under manufacturing contract with Laboratoires Pharmaceutiques Rodael, was approved to supply zinc dispersible tablets (20 mg) to UNICEF. Efforts are now continuing to approve the products of other manufacturers.

Over the last two years, with zinc treatment for the management of acute diarrhoea being included in the policies of more and more countries, some practical issues concerning the supply chain have emerged, including difficulties with product registration in countries.

This document has therefore been prepared to collate and present a summary of current scientific evidence demonstrating the safety and efficacy of zinc treatment in the management of acute diarrhoea, in order to support applications for the registration of zinc in countries for that purpose.

1. Zinc and the treatment of acute diarrhoea

Duration of the episode
With regard to the time from enrolment in the study to recovery from diarrhoea, this review (*4*) shows clearly that zinc treatment has a significant beneficial effect on the clinical course of acute diarrhoea. In 11 of the 12 studies reviewed, administration of zinc was associated with a reduction in the duration of the episode, the reduction being statistically significant in 8 of the 11. From the pooled analysis of these studies, it can be estimated that administration of zinc reduces the duration of diarrhoea by up to 25%.

Proportion of episodes lasting more than seven days
Five studies recorded data on the proportion of episodes lasting more than seven days. The results of all these studies showed a trend towards a reduced proportion of episodes lasting more than seven days in children receiving zinc; in one of the studies, the reduction was statistically significant. Again, the pooled analysis of these studies showed that administration of zinc can reduce the proportion of episodes lasting more than seven days by about 25%, therefore significantly reducing the proportion of diarrhoea episodes that become persistent.

Stool volume
Eight studies collected information on stool volume or frequency. In all of these, zinc treatment was associated with a reduction in stool output/frequency, and in five, the reduction was statistically significant. From these studies, we can estimate that the administration of zinc is associated with a 30% reduction in stool volume.

Based on the results of this review, it was concluded that zinc treatment has a clinically significant beneficial impact on the clinical course of acute diarrhoea, reducing both severity and duration.

2. Zinc and the treatment of persistent diarrhoea

To measure the effect of zinc given with oral rehydration therapy during recovery from persistent diarrhoea, a pooled analysis was performed on the four available published and unpublished randomized controlled trials of the effects of zinc in children under the age of five with persistent diarrhoea (*5*).

Cox regression for survival analysis was used to evaluate the overall effect of zinc on continuation of diarrhoea and possible differential effects in subgroups divided by sex, age, weight-for-height and initial plasma zinc concentration.

Children with persistent diarrhoea who were treated with zinc had a 24% lower probability of continuing diarrhoea (95% confidence interval (CI) 9% - 37%) and a 42% lower rate of treatment failure or death (95% CI 10% - 63%) than those in the control group. It should be noted that there tended to be a greater effect in children less than 12

months of age who were male or who had wasting or lower baseline plasma zinc concentrations.

Overall, the review concluded that zinc treatment reduces the duration and severity of persistent diarrhoea.

3. Zinc and the prevention of acute and persistent diarrhoea

A pooled analysis of randomized controlled trials in children in developing countries (*6*) assessed the effects of zinc administration on the prevention of diarrhoea (acute and persistent). Trials included were those that provided oral supplements containing at least one half of the US Recommended Daily Allowance (RDA) of zinc for children less than five years of age and that evaluated the prevention of serious infectious morbidity through household visits. Analyses included seven "continuous" trials providing a single or double RDA of elemental zinc 5–7 seven times a week throughout the period of morbidity surveillance, and three "short-course" trials providing 2–4 four times the RDA of elemental zinc daily for 2 weeks followed by 2–3 three months of morbidity surveillance. The effects on diarrhoea were analysed overall and in subgroups defined by age, baseline plasma zinc concentration, nutritional status and sex.

In the continuous trials, for the zinc-treated children compared with the control group, diarrhoeal incidence was reduced by 18% (odds ratio (OR) 0.82; 95% CI 0.72–0.93) and prevalence was reduced by 25% (OR 0.75; 95% CI 0.63–0.88). No significant differences were seen in the effects of the zinc between the subgroups.

In the short-course trials, the effects of zinc were similar to those observed in the continuous trials: for the zinc-treated children compared with the control group, diarrhoeal incidence was reduced by 11% (OR 0.89; 95% CI 0.62–1.28) and prevalence was reduced by 34% (OR 0.66; 95% CI 0.52–0.83).

In conclusion, zinc given to children in developing countries, either continuously or as a short-course treatment, is associated with substantial reductions in the rates of diarrhoea.

4. Zinc and the prevention and treatment of bloody diarrhoea

A number of studies have shown that the administration of zinc, either continuous or as a short-course treatment, has a positive impact of the prevalence of dysentery in the following month. In addition, studies conducted during acute shigellosis have shown that the administration of zinc significantly improves seroconversion to shigellacidal antibody response and increases the percentages of circulating B lymphocytes and plasma cells and the IgA-specific immunoglobulin response. For all these reasons, it is clear that zinc should be given as an adjunct to antibiotic treatment of bloody diarrhoea.

5. Zinc and cost–effectiveness evaluation

A recently published study (*7,8*) analysed the incremental costs, effects and cost–effectiveness of zinc used as adjunct therapy to standard treatment of acute childhood diarrhoea, including dysentery, and reassessed the cost–effectiveness of standard case management with oral rehydration therapy. A decision tree was used to model expected clinical outcomes and expected costs under four alternative treatment strategies. 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.

In this study, oral rehydration therapy was found to be less cost-effective than previously thought. The use of zinc as an adjunct, however, significantly improved the cost–effectiveness of standard management of diarrhoea for dysenteric as well as non-dysenteric illness. The results are particularly sensitive to mortality rates in non-dysenteric diarrhoea, but the alternative interventions can be defined as highly cost-effective even in pessimistic scenarios. From this study, there is sufficient evidence to recommend the inclusion of zinc in standard case management of both dysenteric and non-dysenteric acute diarrhoea.

6. Zinc and the irrational use of antibiotics

The excessive use of antibiotics in the treatment of diarrhoea is a major factor contributing to the increasing rates of microbial resistance to antibiotics in developing countries. A study of antibiotic use in a rural area of Bangladesh (*9,10*) found that 26% of purchased drugs were antibiotics, most frequently bought for use against diarrhoea in children aged 0–4 years; 48% of antibiotics were bought in quantities of less than a single day's dose. These practices have probably not led to improvements in health and may have promoted the emergence and persistence of drug-resistant microorganisms. Zinc therapy for diarrhoea has been shown to be beneficial in controlled efficacy trials. It is of interest to determine whether the availability of zinc would satisfy demand for a medicine for diarrhoea, thus reducing the use of antibiotics without competing with the use of oral rehydration therapy.

A community-based controlled trial was conducted in Matlab (Bangladesh), in which 30 service areas (clusters) around Matlab Treatment Centre, each with about 200 children aged 3–59 months, were randomly allocated to intervention or comparison areas. One community health worker served each cluster. All children aged 3–59 months were included in the study. The use of antibiotics for the treatment of diarrhoea was about 70% less in the zinc intervention areas. In addition, visits to pharmacists and village doctors were significantly fewer (such visits are among the most important determinants of inappropriate antibiotic use). The significant reduction in antibiotic use and related behaviour in the intervention group demonstrates that the benefits of zinc treatment

extend well beyond reducing childhood morbidity and mortality. Zinc treatment for diarrhoea plus education programmes, in addition to oral rehydration therapy, could reduce the inappropriate use of antibiotics that is leading to resistance to antimicrobial drugs.

7. Safety of zinc

Zinc is a micronutrient that can be found in all tissues of the body and is essential for cell growth, cell differentiation and DNA synthesis (*11*). It is also essential for the maintenance of a healthy immune system (*12*). Human zinc deficiency was first identified by Prasad et al. in the 1960s in growth-retarded adolescent boys in Egypt (*13*). Recent population level analyses from food balance sheets have estimated that 21% of the world's population is at risk of zinc deficiency (*14*). Children in many developing countries around the world typically consume fewer animal products than adults, especially in the developing world, which results in both stunting and zinc deficiency. A high rate of stunting is considered indicative of zinc deficiency among children less than 5 years of age (*14*). WHO has identified zinc deficiency as a major risk to child health, and has linked it to morbidity from diarrhoea, lower respiratory tract infections and malaria, accounting for 0.8 million child deaths per year (*15*).

The International Zinc Consultative Group (IZiNCG) revised the recommended dietary allowances (RDAs) in 2004 (*16*). These recommendations suggest the following:

Group	RDA of zinc
Infants	4–5 mg
Children 1–3 years of age	3 mg
Children 4–8 years of age	4–5 mg
Non-pregnant women	8–9 mg
Pregnant and lactating women	9–13 mg
Men	13–19 mg

These recommendations take into account differences in diet and are based on a standard reference body weight. Children receiving diets higher in phytate, which is found in unrefined cereals, will need to consume more zinc each day to achieve the physiological requirement. In addition, these guidelines are for healthy children and do not take into account the excess zinc losses during an episode of diarrhoea (*17,18*) or the extra zinc required for catch-up growth and development.

In extensive safety studies undertaken in laboratory animals, zinc has been shown *not* to be carcinogenic, mutagenic or teratogenic (*19*). In addition, the human body has efficient homeostatic mechanisms that regulate the absorption and retention of zinc, and these reduce the likelihood of toxic build-up in the body (*20*). Zinc toxicity in adults can occur following moderately high intakes of zinc (>150 mg/day or approximately 10 times the RDA) over a long period of time or from ingestion of >1 g of zinc (more than 60 times the RDA) by overdose via supplementation or intravenous feeding (*21*). Ingesting too

much zinc at once can cause gastric distress and the typical signs and symptoms often associated with food poisoning.

High doses of zinc for long periods may lead to a lower concentration of plasma lipoproteins and decreased copper absorption (*21*). A lower copper status may also inhibit the transport of iron and result in anaemia (*22*). Although zinc-induced copper deficiency and the resulting anaemia are serious, they occur only after excessive zinc intake over a long period and are easily corrected by adjusting the intake of zinc and copper accordingly (*20*). Supplements of zinc and iron may also compete for absorption in the body.

Cases have been reported of acute, though reversible, adverse reactions from inhaling zinc vapours – a condition known as "zinc fume fever" – and from ingesting food or drink stored in galvanized containers (*20*). There are also a number of reported cases of adverse effects due to excessive zinc intake. The majority of these cases involved adults who knowingly ingested many times the normal daily dose of zinc over a long period. Even in the most extreme cases (more than 1 g/day for many months), patients recovered from all signs and symptoms, including fatigue, gastrointestinal discomfort and anaemia, as soon as zinc intake was decreased and serum zinc returned to the normal range.

In the report of the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, there were 50 cases of adverse effects of oral zinc sulfate, including 56 clinical signs and symptoms. The majority of these cases, involved the patient taking or being given several drugs at the same time, so it was not always possible to identify the cause of the observed sign(s) and/or symptom(s). The cases documented in the report all varied with respect to dosage, patient age, certainty of causality of association and number of additional drugs. There were only 2 reported cases in which the likelihood of causation by zinc was "certain", and only 1 in a child (side-effect: epistaxis) There were 20 reported cases where the likelihood was "possible" and 9 where it was "probable." The level of causation could not be established in the other reported cases. There were four reports of possible adverse responses to zinc ingestion among children less than 10 years of age.

Short-course supplementation trials

After more than 20 years of extensive research, zinc supplementation for the treatment of diarrhoea is now recommended by WHO and UNICEF (*1*). Current recommendations are for 10–14 days of supplementation for all episodes of diarrhoea among children less than 5 years of age. Infants less than 6 months of age are to receive 10 mg daily and children aged between 6 months and 5 years are to receive 20 mg daily. These doses have been proven to be both effective and safe for treatment during diarrhoea.

To date there have been no reports of severe adverse reactions from any form of zinc treatment for diarrhoea. Trials have included more than 9100 children who have participated in efficacy trials in both the placebo and zinc study arms, and nearly 12 000 child-years of observation from one large effectiveness trial. The zinc doses ranged from 5 to 45 mg/day and were well-tolerated in diverse settings. No differences in adverse

reactions were found based on the different zinc salts used in supplementation trials, i.e. the sulfate, acetate and gluconate.

At present, the only reported side-effect of zinc treatment has been vomiting. Of the seven trials that have reported incidences of vomiting, only two reported more vomiting in the zinc-treated children compared with those given a placebo (*23*,*24*). One trial reported more vomiting than in control children when zinc was given with multiple micronutrients but not when given alone (*25*).

Copper status has been evaluated in four trials. In three of these, no difference in serum copper status was found after supplementation (*23*,*26*,*27*). In the fourth trial, a significant trend towards lower copper status was found in zinc-treated compared to untreated children (*28*); however, these children were malnourished with persistent diarrhoea at baseline. Overall, there is no substantial evidence that short-term zinc administration for the treatment of diarrhoea adversely affects copper status.

In addition to trials on the treatment of diarrhoea, there have been several trials assessing the efficacy of zinc for the treatment of pneumonia, malaria, measles and the common cold. Treatments have typically included approximately 20 mg/day for the duration of the illness, which is typically less than two weeks. No serious adverse effects linked to zinc have been reported in these studies.

Long-term supplementation trials

A number of long-term supplementation trials have been carried out among young children and pregnant women. Children have been given zinc supplements to improve growth and to prevent pneumonia, diarrhoea and malaria. In 1999, a review of seven zinc supplementation studies for the prevention of diarrhoea and pneumonia was published (*6*). These trials were conducted in a variety of study populations with different baseline nutritional status. Supplementation with zinc ranged from 5 to 20 mg/day for up to a year. No adverse effects were reported in these studies. There have been two studies in which children were given zinc supplements for the prevention of malaria. Children were given supplements of up to 70 mg zinc, twice a week for up to 15 months, and no adverse effects were reported.

One supplementation trial of low-birth-weight infants demonstrated not only the safety of zinc but the benefits of daily supplementation among these vulnerable babies (*29*). A total of 581 Indian infants aged 30–284 days were each given 5 mg zinc. Those who received the zinc supplementation had a two thirds lower risk of dying over the study period. There were 5 deaths among infants receiving zinc and 15 deaths among infants who did not receive zinc. There were no adverse events linked to zinc supplementation in this trial.

There have been several trials of zinc supplementation among pregnant women (*30*). Because the demands of zinc increase during pregnancy, zinc supplementation may provide benefits to the pregnant mother and the growing fetus, especially in countries where zinc intake is lower than the recommended standards. Although the benefits of providing pregnant women with zinc supplements have yet to be confirmed, there are no

published reports of adverse effects during these trials in either the pregnant women or their infants.

Further studies on zinc supplementation have been completed in the past two years, involving thousands of children who received either 10 mg zinc sulfate per day for up to two years (*31*) or 20 mg zinc sulfate for up to 14 days for the management of acute diarrhoea (*32*). In none of these studies were adverse effects recorded.

Precautions
As with any treatment, zinc supplements should be kept in a safe place to prevent the accidental ingestion of more than the recommended dose. In the unlikely event that a child consumes several zinc supplements, he/she would probably vomit quickly. There is no evidence to suggest that further adverse events would occur but, as in the case of any accidental ingestion of medication, the child should be taken to a health care provider.

Conclusion
Zinc supplementation is a safe and effective treatment for diarrhoea. Zinc has also been shown to be safe in long-term supplementation studies. The most severe adverse effects noted in supplementation trials have been vomiting in some cases and a slight reduction in copper status in some children. Neither has been shown to cause any long-term harm. Although there have been case reports in adults of excessive zinc intake, the adverse effects even in these cases have been limited to short-term morbidity, and few have resulted in any long-term sequelae.

8. Zinc tablets produced by Nutriset

To respond to the research needs expressed by WHO's Department of Child and Adolescent Health and Development, Nutriset and the Laboratoires Pharmaceutiques Rodael (LPR) developed a zinc dispersible tablet for use in infants and young children that was used in various WHO-supported studies (*31–37*). The results of these studies showed that zinc treatment as an adjunct to oral rehydration therapy, is highly effective in reducing the severity and duration of diarrhoea episodes.

Following the results of these studies, which led to the publication of the WHO/UNICEF joint statement on the clinical management of acute diarrhoea (*1*), Nutriset/LPR created ZinCfant®, a zinc dispersible tablet containing 20 mg elemental zinc. This product is identical in composition to the zinc tablets used in the WHO-supported studies. In addition, development of the USP monograph on zinc tablets (*2*) was modelled on the tablets developed by Nutriset/LPR in order to set a norm and thus ensure the quality of the zinc products. Therefore, the zinc tablets produced by Nutriset/LPR are in total concordance with the USP monograph.

It should be noted that the results obtained in the studies mentioned above, using zinc tablets developed by Nutriset/LPR, are similar to results obtained in previous studies in which different zinc products (essentially syrups) were used. From this, we can say that

all the studies presented and discussed in this document form a common basis for a positive evaluation of the risk–benefit ratio of the use of zinc in the management of diarrhoea in children.

9. References

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