Expert Committee on the Selection and Use of Essential Medicines
Geneva, 7-11 March 2005

Application for Addition (zinc sulfate)

Application for the Inclusion of Zinc Sulfate in the WHO Model List of Essential Medicines

SUBMITTED BY:
World Health Organization
Child and Adolescent Health Department

WITH SUPPORT FROM:
Johns Hopkins Bloomberg School of Public Health
USAID
UNICEF

CONTENTS **PAGE**

1. Summary Statement Of The Proposal For Inclusion, Change Or Deletion

Zinc sulfate is proposed for inclusions into the core WHO Model list of essential medicines for the treatment of childhood diarrhea.

2. Name Of The Focal Point In WHO Submitting The Application

Submitted by Dr. Olivier Fontaine on behalf of the World Health Organization, Department of Child and Adolescent Health and Development.

3. Name Of The Organizations Consulted And Supporting The Application

UNICEF, USAID, and The Johns Hopkins Bloomberg School of Public Health

4. International Nonproprietary Name Of The Medicine

Zinc Sulfate

5. Whether Listing Is Requested As An Individual Medicine Or As An Example Of A Therapeutic Group

Zinc sulfate is an essential micronutrient. Listing is requested as an individual medicine.

6. Information Supporting The Public Health Relevance

6.1 Burden of Diarrheal Disease in Children

WHO defines diarrhea as "the passage of loose or watery stools at least 3 times in a 24 hour period". Children in developing countries typically experience up to 6-7 episodes per year whereas children in developed countries only experience 1-2 episodes per year (1). The most common cause of diarrhea in children under five is rotavirus (2). Diarrhea remains a leading cause of death among children in the developing world. In a recently published prediction model which assessed mortality data from the 42 countries with 90% of the child deaths, 22% of under five mortality can be attributed to diarrhea (3). Diarrhea and malnutrition consistently rank in the top 5 causes of childhood deaths (4).

6.2 Global Zinc Deficiency

Individual zinc deficiency is difficult to accurately assess. Population level estimates from national food balance sheets are able to determine the amount of bio-available zinc per person per day by country. These data estimate 21% of persons around the world are at risk of zinc deficiency (5). Because children under the age of 5 typically receive a smaller proportion of high zinc foods, namely meat, at mealtime than adults, this is likely an underestimate for the majority of children in developing countries.

In 2002 the World Health Organization defined zinc deficiency as one of the major risks to child health (6). In this report zinc deficiency was linked to 10% of diarrhea, 6% of lower respiratory tract, and 18% of malaria morbidity and accounts for 0.8 million deaths a year. In addition zinc supplementation programs have been defined as a very cost effective public health intervention (6).

7. Treatment Details

7.1 Overview

Zinc supplementation has been shown to be an effective treatment for acute, persistent, and dysentery diarrhea in children under five (CTRL+click on the author's name to access pdf file of the next three references. If you encounter difficulty contact doccentre@who.int) (Bhutta et al 7, Bhutta et al 8 , Fontaine et al 9). Until recently the only treatment recommended by WHO and UNICEF for non-dysentery acute diarrhea was case management through the use Oral Rehydration Therapy (ORT) or Oral Rehydration Salts (ORS) solution and continued feeding (10). Although the use of ORS/ORT and continued feeding has dramatically decreased mortality from diarrhea deaths in the past 20 years, traditional ORS/ORT does not decrease the duration or severity of the diarrhea episode.

Antibiotics are not recommended for non-cholera, non-dysentery diarrhea; anti-diarrhoeals are never recommended for children under five. However, because ORS/ORT does not treat the episode, caregivers often seek additional treatments and are often incorrectly prescribed antibiotics or anti-diarrhoeals in their effort to help their child's condition. Although these products are globally discouraged, their widespread use is a problem causing unnecessary adverse reactions and increasing rates of antibiotic resistance (10).

Zinc is an essential mineral for human cell growth, differentiation, and DNA synthesis (11). Zinc plays a critical role in the development and maintenance of a healthy immune system (12). There are many associations with diarrhea and increased fecal zinc loss, negative zinc balance, and low tissue zinc concentrations (13). High zinc loss during diarrhea has been observed in infants (14, 15). Zinc supplementation may increase intestinal permeability as demonstrated in children in Bangladesh (16). Zinc supplementation for the treatment of diarrhea may also be critical in improving overall immune function.

7.2 WHO / UNICEF Joint Statement on Clinical Management of Acute Diarrhoea (CTRL+click here for pdf)

WHO and UNICEF have published a joint statement, encouraging widespread use of zinc supplementation for the treatment of childhood diarrhea, in May 2004. This statement recognized the research findings that zinc supplementation can significantly reduce the duration and severity of an episode of diarrhea and if given for 10-14 days will lower the incidence of diarrhea in the subsequent 4-6 months (17). This statement emphasized the responsibility of the health care workers and mothers to treat any child with diarrhea with a 10-14 day daily zinc supplement at a dose of 20 mg/day for children 6-59 months and 10 mg/day for infants less than 6 months of age. The statement goes on to recommend country level promotion of zinc supplementation for the treatment of diarrhea and calls for the support by WHO, UNICEF, and other partners to promote and when needed supply supplements to countries who can not manufacture the high standard supplements.

7.3 Current WHO Recommendations for the Treatment of Diarrhea in Children Under Five

WHO recently updated "The treatment of diarrhea – a manual for physicians and other senior health workers" to include recommendations for the use of zinc.

> '. . it is now recommended that zinc (10-20 mg/day) be given for 14 days to all children with diarrhea.' (18) p. 8)

This document continues to recommend that a health care worker should . .

'Begin to give supplemental zinc, as in Treatment Plan A, as soon as the child is able to eat following the initial four-hour rehydration period." (18) p. 18)

7.4 Summary of Treatment Recommendations

It is recommended by WHO and UNICEF that zinc sulfate be given to all children with diarrhea for 10-14 days.

10 mg/ day	< 6 months of age
20 mg/ day	6 months – 5 years

8. Summary Of Comparative Effectiveness In A Variety Of Clinical Settings

8.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Clinical evidence supporting the use of zinc supplementation for the treatment of diarrhea in children under 5 is vast. Relevant peer reviewed publications were retrieved from a PubMed search using the key words: *zinc AND diarrhea.* Evidence has been limited to randomized controlled trials in children less then 5 years of age. In addition to these trials, 2 pooled analyses are included. The pooled analyses set the standard by which additional studies were included. Later studies which did not meet the strict criteria as described below for these pooled analyses were excluded.

In 2000, Bhutta et al published a pooled analysis of the randomized trials assessing the efficacy of zinc supplementation for the treatment of diarrhea (8). This analysis assessed the duration of diarrhea by using the Cox survival regression model. A meta-analysis of overall effect size was then calculated using the mean and SD of duration of diarrhea in the zinc and control groups.

In a separate pooled analysis, the prevention of diarrhea after zinc supplementation was assessed (7). This analysis included "continuous" trials, when supplementation was given daily throughout the surveillance period, and "short-course" trials, when supplementation was given for 14 days as a treatment for one episode of diarrhea and diarrhea morbidity surveillance continued for some period following. Effects were estimated using the Confidence Profile Method assuming random variability among studies.

Both of these pooled analyses required consistent and standard definitions for acute diarrhea, persistent diarrhea, dysentery, and length of the diarrhea episode. All trials were conducted in developing countries and gave zinc $\geq$ 50% of the US recommended dietary allowance (RDA) (7, 8). In addition, trials that did not define enrollment criteria for the index diarrhea episode were excluded. When possible, the pooled analysis will serve as the summary of trials included in them. Data from trials published after these 2 analyses will then be presented.

8.1.1 Efficacy trials supporting zinc for the treatment of diarrhea

DURATION OF EPISODE
Bhutta et al (8) pooled the results of 3 trials conducted among children with acute diarrhea in India, Indonesia, and Bangladesh (19-21) and that found children who were zinc-supplemented had a 15% lower probability of continuing an episode of diarrhea compared to children not supplemented with zinc (95%CI: 8-22%). When including estimates from 2 additional trials (22, 23), the point estimate remained similar. A subgroup analysis was done by baseline plasma zinc status (above or below the median). Although the pooled effect was greater in the group with the lower baseline plasma zinc, it remained significant in both subgroups (8).

Dutta et al also randomized 80 male children with acute diarrhea between the ages of 3 and 24 months to receive zinc or placebo during hospitalization (24). Zinc-supplemented children had a shorter duration of diarrhea than placebo-supplemented children (70.4 vs. 103.4; p=0.0001). Strand et al assessed the efficacy of 15mg or 30mg daily zinc as a treatment for acute diarrhea in 1792 Nepalese children (25). The zinc-supplemented children had a faster progression to recovery than the placebo-supplemented children (RH 1.26; 95%CI: 1.08-1.46). Al-Sonboli et al randomized 71 children in Brazil to receive 22.5 or 45 mg zinc/day for the treatment of acute diarrhea (26). Children receiving zinc had a shorter duration of diarrhea (1.2 vs. 2.5 days; p<0.001) compared to children not receiving the zinc supplement. Bhatnagar et al randomized 453 boys, 3-36 months of age with acute diarrhea to receive 15mg zinc/day, 30mg zinc/day or a placebo for 14 days (27). Zinc-supplemented boys showed a significant reduction in the duration of the episode when compared to controls (RH for continuation of diarrhea, 0.76; 95%CI: 0.59-0.97).

Bhutta et al (8) also assessed the effect of zinc supplementation on the duration of diarrhea among children presenting with persistent diarrhea in 4 randomized trials conducted in Peru, Bangladesh, and Pakistan (28-31). In these trials, zinc supplemented children had a 24% lower probability of continuing diarrhea (95%CI: 8-38%). One additional trial was added for the random effects estimate which did not change the effect size (32). The subgroup analysis by baseline plasma zinc status had only a significant effect among the lower baseline plasma zinc subgroup. The higher plasma zinc group suggested a positive effect of zinc supplementation, but was not significant (8).

SEVERITY OF EPISODE

The severity of the diarrhea episode was not assessed in the pooled analysis for either acute or persistent diarrhea. Roy et al found a 28% lower median total stool output when comparing zinc supplemented children to control children with acute diarrhea (p=0.06) (20). These differences were more extreme among children with low serum zinc and shorter children. Sazawal et al also observed a 39% decrease in the number of episodes lasting beyond 7 days in zinc-supplemented children when compared with controls (20). Zinc-supplemented children also had a 39% lower mean number of watery stools per day than controls (95%CI: 6-70%). Dutta et al found zinc supplemented children to pass less liquid stool than control children (1.5 vs. 2.4kg; p=0.0001) (24). Strand et al showed a non-significant reduction in the mean number of stools passed in the first 4 days among zinc-supplemented when compared to children receiving placebo (25). Al-Sonboli et al found the mean number of stools per day to be less in the zinc supplemented children when compared to the placebo group (4.1 vs. 10.0; p<0.01) (26). Bhatnagar et al observed a lower total stool output in zinc-supplemented boys compared to controls (ration of geometric means 0.69; 95%CI: 0.48 – 0.99) (27). Faruque et al randomized children presenting with acute diarrhea and assessed severity by the percent of episodes lasting over 7 days (23). Children receiving zinc supplementation had a 43% lower risk of diarrhea continuing past 7 days when compared to controls after adjusting for confounding variables (95%CI: 9-65%).

Sachdev et al observed the overall frequency of stools per day to be lower in the zinc-supplemented children when compared to controls among persistent diarrhea patients (8.8 vs 11.2, non-significant) (32) Khatun et al also observed a lower mean daily stool output from day 2 to day 7 (p=0.034) (29). Children receiving zinc had a 24% lower mean cumulative stool weight on day 7 than controls (p<0.001). No difference was observed in 3 trials of persistent diarrhea cases (28, 31, 32).

TREATMENT FAILURE

Not every trial has analyzed the rates of treatment failure; many are not powered to see a statistically significant difference between the zinc and control group on more severe outcome measures. The pooled analysis of the 4 randomized trials of persistent diarrhea found a 42%

lower rate of treatment failure or death among zinc supplemented children when compared to the controls (95%CI: 10-63%) (8).

ZINC FORTIFIED ORS

A zinc-fortified ORS formula has been tested as a simple mechanism to supplement with zinc while encouraging ORS use (33). Bahl et al randomized 1219 children 6-35 months of age to receive either zinc syrup (15mg for 6-11m or 30mg for 12-35m) or placebo and ORS alone or ORS fortified with 40mg zinc / 1L. ORS was recommended until recovery and syrup during the episode and the following week. Zinc syrup-supplemented children had a lower risk of continuing the diarrhea episode than control children (RH 0.89; 95%CI: 0.8-0.99). The zinc-fortified ORS group did not show a significant improvement in recovery time when compared to controls. Both the zinc syrup-supplemented and the zinc-fortified ORS groups had a decrease in the total number of stools and the proportion of children with watery stools. This study suggests that zinc syrup is more efficacious than zinc-fortified ORS, however zinc-fortified ORS is safe. Zinc-fortified ORS may have been less beneficial than zinc syrup because mothers often do not give the recommended amount of ORS to the child, therefore the zinc dose may have been too low to have an effect.

8.1.2 Efficacy trials supporting zinc for prevention

Bhutta et al (7) (CTRL+click for pdf file) pooled the results of 3 'short-course' supplementation trials in Bangladesh and Pakistan. In all 3 of these trials zinc was given for 20mg / day for 14 days as a treatment for an episode of diarrhea. The children were then followed-up for the following 2-3 months. The pooled effect of supplementation on incidence of diarrhea was non-significant (OR = 0.89). There was a greater pooled effect observed on the prevalence of diarrhea (OR = 0.66; 95%CI: 0.52 – 0.83). One additional trial assessed short course zinc supplementation on diarrhea incidence and prevalence (34). Rahman et al randomized children to receive zinc (20mg daily / 14 days), vitamin A, vitamin A and zinc, or placebo (only zinc alone and placebo are reported here). The incidence rate of diarrhea was 11% less (95%CI: 1-21%) and the prevalence was 18% less (95%CI: 13-22%) in zinc-supplemented children compared to those supplemented with placebo. This study did not show the same positive trend when assessing dysentery.

Bhutte et al (7) also pooled the results of 7 'continuous' supplementation trials in India, Mexico, Papua New Guinea, Peru, Vietnam, Guatemala, and Jamaica. The zinc dose ranged from 5mg – 20mg; the number of supplements per week ranged from 5-7; the number of weeks supplemented ranged from 12-54. All 7 of the trials showed a positive effect of zinc supplementation on the incidence and prevalence of diarrhea during the follow-up period. The result of the pooled OR for diarrheal incidence was 0.82 (95%CI: 0.72 – 0.93). The pooled OR for the pooled assessment on prevalence was 0.75 (95%CI: 0.63 – 0.88). Three trials had data available on dysentery (31, 35-38). The pooled effect on the incidence of dysentery was a non-significant, yet a clinically important 33% reduction in incidence rate.

There have been 5 additional trials assessing continuous zinc supplementation on the incidence and prevalence of diarrhea episodes; a benefit of zinc supplementation was seen in 3 of the 5. Bhandari et al randomized 2482 Indian children 6-30 months of age to receive daily zinc (10 or 20mg) or placebo for 4 months (39). The incidence of diarrhea was 12% lower (95%CI: 5-18%) in the zinc-supplemented children compared to the children receiving the placebo. The benefit of the zinc became greater when analysis were done on the diarrhea episodes lasting over 14 days and on the diarrhea episodes with more than 10 stools per day. A study of 280 children 6-41 months of age in India showed a positive impact of zinc supplementation for 16 weeks (40). Children received 10mg zinc/day for 5 days of the week, one 50mg dose per week, or placebo. A lower proportion of children in both zinc-

supplemented groups had any diarrhea during the follow-up periods (15.8 and 16.5% compared to 30.8%, $p<0.05$). The diarrhea incidence rate was lower in zinc-supplemented children (RR = 0.41; 95%CI: 0.24 – 0.71). Sur et al randomized 100 low birth weight infants to receive daily zinc (5mg) or placebo from birth to one year of age (41). Weekly surveillance found that zinc-supplemented infants had 1.36 episodes of diarrhea in that year whereas placebo-supplemented infants had 1.93 episodes / year (RR = 1.4; 95%CI: 1.02 – 2.0).

Two trials found no different in the incidence or prevalence of diarrhea among zinc- or placebo-supplemented infants. Osendarp et al supplemented infants from 4 weeks of age to 24 weeks of age with 5mg zinc/day or placebo (42). There was a trend toward a positive effect among zinc deficient children, thus this population of young, healthy infants may not have been deficient enough to see a benefit. Baqui et al (43) randomized infants at 6 months of age to receive weekly supplementation until 12 months of age. There was no difference in the incidence of diarrhea among children supplemented weekly with 20mg zinc + 1mg riboflavin compared to those supplemented with riboflavin alone.

8.2 Summary of available data (appraisal of quality, outcome measures, summary of results)

The available data to support the use of zinc supplementation for the treatment of diarrhea are conclusive. There are numerous well-designed randomized controlled trials in thousands of children which clearly show zinc to be an effective treatment for diarrhea. Typically studies have assessed the duration of the diarrhea both as observed in the hospital and as reported by the mother during frequent home interviews. Hospital based studies may be the best was to assess an accurate endpoint of diarrhea, but studies which gather this data from a mother reporting to a health worker are more realistic and representative of what will happen when zinc is introduced globally. The results from these studies are clear. Zinc is an effective treatment for diarrhea in children under 5 and should be recommended by health care personnel in all developing countries. The World Health Organization should support this by including zinc on the essential medicines list.

8.3 Summary of available estimates of comparative effectiveness

Zinc sulfate doe not take the place of any other drug or treatment. There are currently no drugs or treatments recommended for acute diarrhea in children under 5 other than ORS/ORT. Zinc is not meant to replace ORS/ORT, but will be recommended in addition to it.

One trial to date has assessed zinc supplementation in a cluster randomized design to provide information on the effectiveness of zinc when made available in the community, giving mothers the freedom of choice when with regard to diarrhea treatment (44). Thirty community clusters were randomized to either zinc (recommended as a 20 mg/day/14 day) or not. Community health workers were trained to treat diarrhea according to the randomization scheme. There were 11,881 child years of observation. The percent of episodes treated with zinc in the zinc clusters rose to 80% by the 7^{th} month of the study and remained constant throughout the rest of the study. In the 1252 episodes of diarrhea which were followed, the duration was 24% lower in children living in the zinc clusters (95%CI: 10-30%). Overall incidence of diarrhea during the study period was 15% lower (95%CI: 4-24%), diarrhea related hospital admissions were 24% lower (95%CI: 2-41%), and non-injury mortality was 51% lower (95%CI: 6-75%) in the zinc clusters when compared to control clusters. This study assessed the effectiveness of zinc when incorporated into an existing health system and found similar findings as the controlled efficacy studies. These data confirm that zinc can be a simple addition to diarrhea control programs and efficacy can be expected to remain exceptional.

9. Summary of comparative evidence on safety

9.1 Estimate of total patient exposure to date

Seventeen published clinical trials in over 8,500 children less than five years of age and one large cluster randomized trail of near 12,000 child years of observation indicate that up to 20 mg of zinc given as a 14 day supplement is well-tolerated and does not present significant adverse reactions.

The published trials to date have supplemented infants and children, 3-59 months of age with zinc from 5mg – 45 mg daily. Trials have used zinc sulfate, acetate, and gluconate. There are no published differences of adverse reaction based on zinc salt differences and no published severe adverse reactions for any form of zinc supplement in these trials.

9.2 Description of adverse effects/reactions

9.2.1 Clinical trials published to date

The most commonly reported adverse reaction in trials to date is vomiting. Among the trials that published information regarding vomiting, it was rarely severe and limited to a few patients. Three trials noted that there was no significant difference in vomiting among zinc supplemented children when compared to controls (25-27). One trial had a higher proportion of children vomit in the zinc syrup-supplemented (38.3%) compared with the placebo (26.3%) (33). Among zinc supplemented children reporting vomiting, the mean number of episodes was 0.5 per day, the vomiting observed in this trial was not severe. A trial in Jamaica reported no statistical difference in the number of children reporting vomiting in zinc compared with placebo, but did observe zinc supplemented children to vomit longer on average than the non-zinc supplemented children (2 days vs. 1 day) (45). An earlier trial by Penny et al (31) did not observe the same effect. In this trial, the highest proportion of children reporting vomiting was seen in the placebo group.

Hospitalizations for any reason may be one way to detect adverse events that may or may not be linked to the zinc supplementation. Thus far there have been no studies reporting an increase in hospitalizations among zinc-supplemented children, in fact the opposite is observed. In a trial published in 1998 by Meeks Gardner et al (45) there were 5 children hospitalized during the study period. All 5 of these children were from the placebo group; this difference was statistically significant ($p=0.02$). Roy et al observed a trend of zinc supplementation being protective against death (30). In this trial of 190 children with persistent diarrhea, 5 children died from the control group and one from the zinc-supplemented group.

9.2.2 Risk of copper deficiency

One potential risk of excess zinc intake is copper deficiency. Metabolic studies in adults have shown mixed results after long term increases in dietary and supplementary zinc (46, 47). Although long-term supplementation of large zinc quantities may not be healthy for serum copper status, the dose and duration of supplementation proposed does not appear to have any negative effect on copper status. Two trials assessed copper status and found no difference in mean serum copper levels between zinc-supplemented and placebo-supplemented children after 14 days of supplementation (25, 27).

9.2.3 Summary of adverse events recorded by the Upsala Monitoring Centre

The WHO Collaborating Centre for International Drug Monitoring summary for oral zinc sulfate included 50 reports of 56 clinical signs and symptoms. The majority of the reports documented multiple drugs given to the patient at the time. The doses of zinc, patient age, certainty of causality of association, and number of additional drugs varied. Six reports had more than one suspected drug; 14 additional reports recorded additional medications taken at the time. Only 2 reported "certain" as the likelihood of causation by zinc; 20 reported "possible" causation; 9 reported "probably" as causation; others did not report a level of causation.

There were 4 reports among children under 10 years of age. These are summarized below:

A. 5 ml of oral zinc given to a 4 years old boy for 3 days. Adverse effect, dysuria, reported as being 'unlikely' linked to zinc sulfate.
B. Undefined dose of oral zinc given to a 6 year boy. Adverse effect, epistaxis, reported as being 'certainly' linked to zinc sulfate.
C. 50mg or oral zinc / day for an undefined length of time. Adverse events reported include rash, pruritus, and vomiting with 'non-defined' links to the certain causative drug and multiple drugs suspect.
D. 9 mg of oral zinc given to a 9 year old for an undefined length of time. Adverse event, headache and nausea, with 'non-defined' links to zinc sulfate.

9.3 Identification of variation in safety due to health systems and patient factors

9.3.1 Health system

Zinc has been studied in a variety of treatment trial settings: in-patient hospitals, outpatient hospitals or clinics, and community settings. There has been no variation in safety due to differences in persons administering the supplement or setting variation. In a hospital-administered setting, medical personnel may administer the supplement, but often the supplement is given to the mother to administer. The supplements are easy to give a small child, thus in-patient and home-based settings have both had successful results. The study by Baqui et al (44) was a large scale effectiveness trial where zinc was made available in chosen clusters through the typical routes by which mothers would seek health care for a diarrhea episode in a child under 5.

Ensuring that zinc is available to the people through the health system that they typically seek treatment for diarrhea is important. There is no evidence to suggest that this will increase adverse events.

9.3.2 Patient Factors

AGE:
All published trials have been conducted in children between the ages of 3 and 60 months. The data support the supplementation of all children with diarrhea regardless of age. Individual studies have reported slight variation in the efficacy of the zinc supplements when stratifying by age, but these data are merely slight variations in the efficacy and not in any way evidence to limit supplementation. One meta analysis showed very slight variation in the point relative hazard and the effect size when assessing the effect of supplementation in children with acute diarrhea who are < 12 months and > 12 months separately. This

difference was slightly greater among children with persistent diarrhea. In persistent diarrhea cases, a statistically significant effect was seen among children < 12 months of age, but was not seen in children > 12 months of age (8).

One study supplemented male infants 1-6 months of age in Bangladesh (48). This study has not been published but the results concerning the safety of supplementation in this very young infant age group are important. Two hundred and seventy five hospitalized infants with acute diarrhea were randomized to receive daily 5mg zinc, 20 mg zinc, or placebo for the duration of the illness. A higher proportion of zinc-supplemented infants experienced vomiting at some point during the study, but this was not statistically higher than the placebo-supplemented infants. However, when vomiting did occur, the 5 mg zinc-supplemented infants had a statistically significant lower frequency of vomiting and the 20mg zinc-supplemented babies had a smaller volume of vomit than the placebo-supplemented babies. These data support the conclusion that zinc supplementation for the treatment of diarrhea is safe among all children and can be safely used and recommended in children 1 month to 5 years of age. Currently there is a larger study being conducted in Ethiopia, India, and Pakistan among babies 1- 6 months of age. This multi-site study is assessing the efficacy and safety of 10 mg / day for 14 days in babies with acute diarrhea; results will be made available in 2005.

NUTRITIONAL STATUS:
All trials have been done in developing countries where children with a variety of anthropometric measurements present for treatment and enrollment. Some trials have specifically targeted stunted or wasted children (24, 28, 45), but the majority have enrolled all children, excluding only those by which extremely poor nutritional status warrants a higher level of care than a study is able to give. One meta analysis showed zinc supplementation to have a slightly stronger effect among wasted persistent diarrhea patients when compared to wasted controls than non-wasted persistent diarrhea patients when compared to non-wasted controls (8). When stratified by nutritional status, there is no difference in safety of zinc supplementation.

9.4 Summary of comparative safety against comparators

Oral Rehydration Salts solution is the cornerstone of the recommended case management strategy for common episodes of diarrhea. The efficacy/safety of ORS is not questioned. Zinc is not meant to replace ORS, but meant to enhance and encourage the use of ORS.

Antibiotics may be appropriately recommended for cholera and dysentery diarrhea, but are commonly also prescribed and available for all forms of diarrhea. For dysentery or cholera, zinc is not meant to replace antibiotic treatment, but can be given in addition to antibiotic therapy and ORS. For episodes, which do not require the use of antibiotics, zinc will provide a more effective and safer alternative than antibiotics. The need for alternatives to discourage the inappropriate use of antibiotics is great (10). Marketing strategies are under way to develop messages for the promotion of zinc therapy to treat diarrhea and to be prescribed and used instead of antibiotics for most cases of diarrhea.

10. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

10.1 Range of costs of zinc sulfate

Zinc sulfate is an essential micronutrient; therefore it does not have drug patents which must be overcome to make it available in the developing world. Zinc supplements in tablet and syrup

form have been made in Bangladesh and India for local trials. For the most recent trials, Nutriset/Rodael, a French Pharmaceutical Company, has been the primary supplier for large scale multi-country trials on multiple continents.

Nutriset/Rodael has developed a tablet containing 20 mg of elemental zinc and that can be dispersed in less than 30 seconds in a few ml of water. Acceptability of these tablets has been extensively tested in many developing countries and found to be excellent. The zinc tablets can be provided in blister packs of 10 to 15 tablets at a cost of approximately Usct1.00 per tablet. One blister pack is recommended for one episode of diarrhea.

Nutriset/Rodael has agreed to transfer technology to any country which wishes to start local production of these zinc dispersible tablets. The capacity for large-scale zinc production may not be available immediately in many countries, but the possibility of technology transfer keeps this a viable option for the future and something countries can work towards manufacturing at the local level. In Bangladesh large scale manufacturing is under way.

In many countries zinc syrups are already available commercially. In these countries this could be used instead of tablets. However, usually the cost of syrups is higher than the cost of tablets.

Zinc is an effective treatment for diarrhea, and it is also a treatment affordable to the poorest of the poor. The low cost is one of the added benefits of zinc supplements; new suppliers will have to maintain high quality while keeping costs low.

Local level prices must be determined at the country or local level. Zinc sulfate supplements should be affordable and available to children with diarrhea, but respect for the value as a treatment must be maintained. Zinc may be made available free of charge to some populations, while others are charged a small price. Local determination of the best price to increase use will be used to help determine local pricing schemes.

10.2 Comparative cost-effectiveness presented as range of cost per routine outcome

The cost of the correct treatment of diarrhea varies depending on the type of diarrhea. Simple diarrhea should only be treated with ORS and zinc supplementation. Dysentery or cholera requires the use of an antibiotic. The tables below allow for a cost analysis of the recommended treatments for all diarrhea episodes compared to non-recommended treatments based on median agency prices for ORS and anti-diarrhoeals and supplier price for antibiotics as reported by the International Drug Price Indicator Guide (49). Although never recommended, anti-diarrhoeals are often self-prescribed and add to the total cost of an episode of diarrhea.

Treatment	**Dose**	**Price per dose**	**# needed per diarrhea episode**	**Total Cost**
Zinc	20 mg	$ 0.01	1 packet	$ 0.14
ORS	1/day	$ 0.06	5 packets	$ 0.30
				$ 0.44

Table 1. Cost of proper treatment of non-dysentery diarrhea for 5 days

Table 2. Cost of improper treatment of non-dysentery diarrhea for 5 days

Treatment	Dose	Price per dose	# needed per diarrhea episode	Total Cost
ORS	1/day	$ 0.06	5 packets	$ 0.30
Loperamide	2mg	$ 0.0164	1 tablet X 5 / day X 5 days = 25	$ 0.41
Ampicillin	250mg	$ 0.0174	1 tablet X 2/ day X 7 days = 14	$ 0.54
				$ 1.25

Treatment	Dose	Price per dose	# needed per diarrhea episode	Total Cost
Zinc	20mg	$ 0.01	1 packet	$ 0.14
Ciprofloxacin	500mg	$ 0.021	1 tablet X 2/ day X 3 days = 6	$ 0.13
ORS	1/day	$ 0.06	5 packets	$ 0.30
				$ 0.57

Table 3. Cost of proper treatment of dysentery diarrhea for 5 days

Zinc supplementation will remain a cost effective treatment for diarrhea. Not only does it have therapeutic benefits for a lower price than using anti-diarrhoeals and incorrectly using antibiotics, but it also has the potential to serve as a substitute therapy. Mothers want to give their babies a treatment and often something more than ORS. When zinc is prescribed, mothers have a cost effective option that may discourage them from buying additional unneeded and possibly dangerous antibiotics and anti-diarrhoeals.

11. Availability of pharmacopoieal standard

British Pharmacopoeia No
International Pharmacopoeia Requested
United States Pharmacopoeia Specification under development

12. Proposed text for the WHO Model Formulary

17.7.3 Gastrointestinal Medicines, Medicines Used in Diarrhea

Zinc Sulfate is an essential micronutrient and is an effective treatment for childhood diarrhea.

Zinc Sulfate
Tablets, Zinc sulfate 10mg; 20mg
Uses: acute and persistent diarrhea in children less than 5 years of age
Contraindications
Precautions:
Interactions:
Dosage: Diarrhea in INFANTS less than 6 months of age, *by mouth*, 10mg tablet dispersed in small amount of breast milk, ORS or water, daily for 14 days; CHILDREN 6 months – 5 years of age, *by mouth*, 20mg dispersed in a small amount of breast milk, ORS or water, or chewed.
Adverse Effects: vomiting, nausea

14. References

1. Santosham M, Keenan EM, Tulloch J, Broun D, Glass R. Oral rehydration therapy for diarrhea: an example of reverse transfer of technology. Pediatrics 1997;100:E10.
2. Black RE. Diarrheal diseases. In: Nelson KE, Williams CM, Graham NMH, eds. Infectious disease epidemiology. Gaithersburg: Aspen Publishers, 2000.
3. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? Lancet 2003;361:2226-34.
4. Rice AL, Sacco L, Hyder A, Black RE. Malnutrition as an underlying cause of childhood deaths associated with infectious diseases in developing countries. Bull World Health Organ 2000;78:1207-21.
5. Brown KH, Rivera JA, Bhutta Z, et al. Assessment of the risk of zinc deficiency in populations. Food and Nutrition Bulletin 2004;25:S130-162.
6. WHO. World Health Report 2002: Reducing risks, promoting healthy life. Geneva: World Health Organization, 2002.
7. Bhutta ZA, Black RE, Brown KH, et al. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. Zinc Investigators' Collaborative Group. J Pediatr 1999;135:689-97.
8. Bhutta ZA, Bird SM, Black RE, et al. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. Am J Clin Nutr 2000;72:1516-22.
9. Fontaine O. Effect of zinc supplementation on clinical course of acute diarrhoea. J Health Popul Nutr 2001;19:339-46.
10. Claeson M, Merson MH. Global progress in the control of diarrheal diseases. Pediatr Infect Dis J 1990;9:345-55.
11. Sandstead HH. Zinc deficiency. A public health problem? Am J Dis Child 1991;145:853-9.
12. WHO. Zinc. In: WHO, ed. Trace elements in human nutrition and health. Geneva: WHO, 1996.
13. Hambidge KM. Zinc and diarrhea. Acta Paediatr Suppl 1992;381:82-6.
14. Zinc and copper wastage during acute diarrhea. Nutr Rev 1990;48:19-22.
15. Castillo-Duran C, Vial P, Uauy R. Trace mineral balance during acute diarrhea in infants. J Pediatr 1988;113:452-7.
16. Roy SK, Behrens RH, Haider R, et al. Impact of zinc supplementation on intestinal permeability in Bangladeshi children with acute diarrhoea and persistent diarrhoea syndrome. J Pediatr Gastroenterol Nutr 1992;15:289-96.
17. WHO, UNICEF. WHO-UNICEF Joint statement on the clinical management of acute diarrhea. World Health Assembly. Geneva, 2004.
18. WHO. The treatment of diarrheoa: a manual for physicians and other senior health workers. Geneva: WHO, 2003.
19. Sazawal S, Black RE, Bhan MK, Bhandari N, Sinha A, Jalla S. Zinc supplementation in young children with acute diarrhea in India. N Engl J Med 1995;333:839-44.
20. Roy SK, Tomkins AM, Akramuzzaman SM, et al. Randomised controlled trial of zinc supplementation in malnourished Bangladeshi children with acute diarrhoea. Arch Dis Child 1997;77:196-200.
21. Hidayat A, Achadi A, Sunoto, Soedarmo SP. The effect of zinc supplementation in children under three years of age with acute diarrhea in Indonesia. Med J Indonesia 1998;7:237-41.

22. Sachdev HP, Mittal NK, Mittal SK, Yadav HS. A controlled trial on utility of oral zinc supplementation in acute dehydrating diarrhea in infants. J Pediatr Gastroenterol Nutr 1988;7:877-81.
23. Faruque AS, Mahalanabis D, Haque SS, Fuchs GJ, Habte D. Double-blind, randomized, controlled trial of zinc or vitamin A supplementation in young children with acute diarrhoea. Acta Paediatr 1999;88:154-60.
24. Dutta P, Mitra U, Datta A, et al. Impact of zinc supplementation in malnourished children with acute watery diarrhoea. J Trop Pediatr 2000;46:259-63.
25. Strand TA, Chandyo RK, Bahl R, et al. Effectiveness and efficacy of zinc for the treatment of acute diarrhea in young children. Pediatrics 2002;109:898-903.
26. Al-Sonboli N, Gurgel RQ, Shenkin A, Hart CA, Cuevas LE. Zinc supplementation in Brazilian children with acute diarrhoea. Ann Trop Paediatr 2003;23:3-8.
27. Bhatnagar S, Bahl R, Sharma PK, Kumar GT, Saxena SK, Bhan MK. Zinc with oral rehydration therapy reduces stool output and duration of diarrhea in hospitalized children: a randomized controlled trial. J Pediatr Gastroenterol Nutr 2004;38:34-40.
28. Bhutta ZA, Nizami SQ, Isani Z. Zinc supplementation in malnourished children with persistent diarrhea in Pakistan. Pediatrics 1999;103:e42.
29. Khatun UH, Malek MA, Black RE, et al. A randomized controlled clinical trial of zinc, vitamin A or both in undernourished children with persistent diarrhea in Bangladesh. Acta Paediatr 2001;90:376-80.
30. Roy SK, Tomkins AM, Mahalanabis D, et al. Impact of zinc supplementation on persistent diarrhoea in malnourished Bangladeshi children. Acta Paediatr 1998;87:1235-9.
31. Penny ME, Peerson JM, Marin RM, et al. Randomized, community-based trial of the effect of zinc supplementation, with and without other micronutrients, on the duration of persistent childhood diarrhea in Lima, Peru. J Pediatr 1999;135:208-17.
32. Sachdev HP, Mittal NK, Yadav HS. Oral zinc supplementation in persistent diarrhoea in infants. Ann Trop Paediatr 1990;10:63-9.
33. Bahl R, Bhandari N, Saksena M, et al. Efficacy of zinc-fortified oral rehydration solution in 6- to 35-month-old children with acute diarrhea. J Pediatr 2002;141:677-82.
34. Rahman MM, Vermund SH, Wahed MA, Fuchs GJ, Baqui AH, Alvarez JO. Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. BMJ 2001;323:314-8.
35. Ninh NX, Thissen JP, Collette L, Gerard G, Khoi HH, Ketelslegers JM. Zinc supplementation increases growth and circulating insulin-like growth factor I (IGF-I) in growth-retarded Vietnamese children. Am J Clin Nutr 1996;63:514-9.
36. Sazawal S, Black RE, Bhan MK, et al. Zinc supplementation reduces the incidence of persistent diarrhea and dysentery among low socioeconomic children in India. J Nutr 1996;126:443-50.
37. Sazawal S, Black RE, Bhan MK, Jalla S, Sinha A, Bhandari N. Efficacy of zinc supplementation in reducing the incidence and prevalence of acute diarrhea--a community-based, double-blind, controlled trial. Am J Clin Nutr 1997;66:413-8.
38. Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A, Bhan MK. Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double-blind, controlled trial. Pediatrics 1998;102:1-5.
39. Bhandari N, Bahl R, Taneja S, et al. Substantial reduction in severe diarrheal morbidity by daily zinc supplementation in young north Indian children. Pediatrics 2002;109:e86.

40. Gupta DN, Mondal SK, Ghosh S, Rajendran K, Sur D, Manna B. Impact of zinc supplementation on diarrhoeal morbidity in rural children of West Bengal, India. Acta Paediatr 2003;92:531-6.
41. Sur D, Gupta DN, Mondal SK, et al. Impact of zinc supplementation on diarrheal morbidity and growth pattern of low birth weight infants in Kolkata, India: a randomized, double-blind, placebo-controlled, community-based study. Pediatrics 2003;112:1327-32.
42. Osendarp SJ, Santosham M, Black RE, Wahed MA, van Raaij JM, Fuchs GJ. Effect of zinc supplementation between 1 and 6 mo of life on growth and morbidity of Bangladeshi infants in urban slums. Am J Clin Nutr 2002;76:1401-8.
43. Baqui AH, Zaman K, Persson LA, et al. Simultaneous weekly supplementation of iron and zinc is associated with lower morbidity due to diarrhea and acute lower respiratory infection in Bangladeshi infants. J Nutr 2003;133:4150-7.
44. Baqui AH, Black RE, El Arifeen S, et al. Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. BMJ 2002;325:1059.
45. Meeks Gardner J, Witter MM, Ramdath DD. Zinc supplementation: effects on the growth and morbidity of undernourished Jamaican children. Eur J Clin Nutr 1998;52:34-9.
46. Taper LJ, Hinners ML, Ritchey SJ. Effects of zinc intake on copper balance in adult females. Am J Clin Nutr 1980;33:1077-82.
47. Festa MD, Anderson HL, Dowdy RP, Ellersieck MR. Effect of zinc intake on copper excretion and retention in men. Am J Clin Nutr 1985;41:285-92.
48. Brooks WA, Santosham M, Roy SK, et al. Efficacy of zinc supplementation in young infants with acute watery diarrhoea. Submitted.
49. Health MSF. International Drug Price Indicator Guide. Electronic Resource Center, 2004.