

# Zinc Supplementation for the Treatment of Diarrhea

## Moving from Research to Practice

### The History of ORS and the Inclusion of Zinc Supplementation

Over two million children die as a result of diarrhea and dehydration every year. In the majority of cases, diarrhea is preventable through exclusive breastfeeding, improved hygiene and sanitation, and access to clean water, yet it is still one of the leading causes of death among children under five. A new Oral Rehydration Solution (ORS) formula and the introduction of zinc supplementation offer much improved outcomes for the treatment of childhood diarrhea. The introduction of zinc supplementation in diarrhea treatment provides for a high impact child survival intervention.

In the early 1980s, the introduction of ORS led to significant and continuing decreases in the rate of diarrhea mortality that lasted for more than 20 years. Until recently, ORS, increased fluids, and continued feeding have been the only recommended treatments for episodes of non-complicated diarrhea. Even though the accepted ORS formula was proven effective, researchers continued to work on developing an improved formula that would allow for more hydration while decreasing the amount of stool output. As a result, an ORS formula with lower glucose and sodium concentrations was developed, and it has proven to be more effective by decreasing the need for intravenous therapy, decreasing stool output, and decreasing the rate of vomiting.<sup>1</sup> This new formula is recommended as one part of an improved diarrhea therapy and treatment.<sup>2</sup> Zinc is another part.

Zinc is an essential micronutrient for human growth, development, and maintenance of the immune system. The first cases of zinc deficiency were recognized in the 1960s in adolescent boys in Egypt who suffered from growth retardation.<sup>3</sup> A recent assessment by the International Zinc Consultative Group estimated that 20% of the world's population is at risk of inadequate zinc intake.<sup>4</sup> In addition, high levels of zinc are lost in the stools during diarrhea episodes.

For more than 20 years, researchers have assessed the benefit of zinc supplementation during diarrhea episodes. A meta-analysis of eight trials of acute and persistent

diarrhea found a 15% reduction in the duration of acute diarrhea and a 24% reduction in the duration of persistent diarrhea among children receiving zinc supplementation when compared to children who received a placebo.<sup>5</sup> These studies also revealed that children receiving zinc supplementation experienced a decrease in the severity of their diarrhea episodes. Children who received 10–14 days of zinc supplementation also showed greater resistance to episodes of diarrhea and other infectious diseases for the 2–3 month period following treatment.<sup>6</sup> Eleven additional trials have confirmed these results, supporting the inclusion of 10–14 days of 10–20 mg of zinc supplementation as another element in the recommended diarrhea therapy.

### Bangladesh Study Provides Proof of Zinc's Benefits

A two-year, community-based trial in rural Bangladesh, which included 30 health worker areas and nearly 12,000 child years of observation, further proved that zinc supplementation is effective in the treatment of diarrhea. Children living in areas where zinc supplementation was recommended in conjunction with ORS therapy had a 23% shorter duration of diarrhea episodes than children living in areas where ORS therapy alone was the accepted treatment. The children living in zinc-supplemented areas also experienced a shorter duration of persistent diarrhea illness, fewer days of illness attributed to acute lower respiratory infections, and fewer hospitalizations. Furthermore, in areas where zinc was included with ORS, the ORS use rates increased, while hospitalizations and the unnecessary use of antibiotics decreased. Perhaps most importantly, in zinc-supplemented areas, children had a 51% lower risk of non-injury related deaths compared to children living in areas where zinc was not available. This study confirms that zinc supplementation in a community setting is an effective treatment for childhood diarrhea and continues to improve child health in the months immediately following diarrhea episodes.

WHO and UNICEF now recommend the use of low osmolarity ORS for the correction and prevention of

dehydration and 10–20 mg of zinc for 10–14 days as treatment for all episodes of diarrhea. With the widespread use of this effective treatment combination, up to 88% of diarrhea deaths can be prevented.<sup>7</sup>

*“Many more lives can be saved if these advances are used in conjunction with effective home treatments and the use of appropriate health services, and to be most effective, these revised recommendations must become routine practice both in the home and the health facility.”<sup>8</sup>*

The combined recommendation of zinc and ORS is a safe, effective, and inexpensive treatment for children in the developing world. The only known side effect of zinc supplementation is vomiting; which is rarely reported and is typically attributed to a metallic taste in the supplement. Use of high-quality supplements can easily avert this side effect. ORS is now safer than ever because the lower osmolarity decreases the likelihood of hypertonicity on net fluid absorption.

Zinc supplements require simple technology and no expensive ingredients. The tablets used in research trials were developed and patented by Nutriset/Rodale (France) and sold to trials for \$0.14 per 14-tablet blister pack. Efforts are already underway to transfer the technology to local manufacturers in the developing world, who will be able to take over the production of tablets, thus keeping costs affordable for the poorest of the poor. ORS has always been an inexpensive treatment for dehydration.

#### **Case Study: Bougouni District, Mali**

A study in Mali is currently assessing two different distribution strategies before scaling up zinc countrywide. In rural Mali, when a child has diarrhea, parents frequently first treat with traditional medications or antibiotics available within the village. Generally, only if the child’s condition worsens do they seek care at a community health center facility where ORS and other treatments can be bought. For this reason, having zinc supplements available, along with ORS, in village drug kits (managed by community health workers) may prove to be an important strategy in ensuring adequate coverage and better diarrhea treatment in rural villages.

## **Ensuring the Use of Zinc in the Treatment of Diarrhea**

It is now the responsibility of the global community to ensure that zinc is used to treat every diarrhea episode in children under 5. There are several challenges that must be overcome to make this possible.

### **Programmatic Challenge Points:**

1. International and national level product availability
2. National and local level product coverage
3. Health worker/physician training and endorsement
4. Home-based treatment compliance

Zinc supplements are the new addition to diarrhea treatment. Recommendations for zinc treatment are always given in conjunction with ORS and continued feeding. Introducing a new treatment, such as zinc, creates an opportunity to energize current diarrhea training programs and provides an excellent opportunity to design enhanced or new programs where needed. This new treatment will increase ORS use rates and improve continued feeding practices.

### **Programmatic Challenge Points**

1. International and national level product availability. To date, dispersible tablets of zinc sulphate packaged in blister packs of 10–14 tablets have been the most commonly used form of zinc supplementation. The tablets are inexpensive, easy to transport and carry, and are accepted by both mothers and children. Nutriset/Rodale developed the simple technology needed to produce these tablets and has been the primary supplier for research and small start-up programs. Technology transfer to local manufacturers is available and is currently underway in Bangladesh. Similar technology has been developed, and production is expected shortly in India. The global demand for dispersible zinc tablets is expected to be great. Increasing the number of global suppliers will be vital for programmatic expansion. Zinc is an essential micronutrient and may be available in local formulations. A careful assessment of the quality and consistency of currently available zinc products, which may include varieties of local tablets and syrups, should be complete before programmatic endorsement and promotion occur. Continuous monitoring of product quality may be needed to ensure children are receiving safe and effective zinc supplementation for the treatment of diarrhea.
2. National and local level product coverage. Ensuring zinc supplements reach local level health clinics and health care providers will require the endorsement and commitment of national and local level governments by either providing financial backing or accepting and endorsing USAID missions and other aid agencies to procure and distribute zinc products. In many countries, multiple level

partnerships with local aid agencies will be necessary to achieve the highest product coverage rates in all areas of the country. There are many country-level decisions regarding the sale and/or dispersal of zinc supplements in addition to ORS. Zinc and ORS are to be recommended together, zinc should never be promoted as a substitute of ORS. Ideally, zinc and ORS supplies would always be given or sold in the same location. Zinc is an essential micronutrient and not a drug, per se, though some countries may take a different stance on this, which may have an impact on where zinc is available and who is permitted to sell or give zinc supplements to patients.

3. Health worker/physician training and endorsement. Healthcare worker and physician endorsement and promotion are crucial if zinc is to be used for every childhood diarrhea episode. Introducing zinc in training courses for both private and public health sector providers presents an excellent opportunity to review the basic diarrhea control strategies including diarrhea prevention, dehydration treatment with ORS and increased fluids, and continued feeding during illness. Special attention should be given to providers who are the most common source of diarrhea treatment care. These providers will be directly responsible for the promotion of zinc for sick children. Physicians giving higher-level medical care should also understand and support zinc treatment to add the needed validity and support as the country's child health experts.
4. Home-based treatment compliance. Healthcare workers who are well trained in the basic diarrhea treatment protocol will soon be recommending zinc for all childhood diarrhea episodes. These providers have a unique one-on-one opportunity to influence the compliance to treatment recommendations by informing and teaching mothers home-based diarrhea therapy including zinc supplements and ORS use. Acceptance and willingness to give zinc supplements for diarrhea may also be influenced by national and local level promotion efforts. Social marketing campaigns to promote the correct use of zinc supplements will influence the acceptability of zinc as part of a new complete diarrhea treatment strategy. Consistently encouraging zinc in addition to ORS through marketing campaigns will be an effective way to promote the use of the simultaneous and correct use of both treatments.

#### **Case Study: Scaling Up Zinc In Young Children (SUZY) Project, Bangladesh**

Bangladesh was the site of many zinc and diarrhea research studies and is now taking the lead in developing a countrywide program to have zinc available, promoted, and used for all diarrhea episodes. As part of the process of scaling-up, the SUZY Project identified a brand name for zinc and hired local advertising agencies to lead a mass media marketing campaign to promote zinc as part of the new diarrhea treatment strategy.

## **Cost and Sustainability**

The cost of treating a child for an episode of diarrhea is dependent on the severity of the episode. While some countries may determine that selling zinc supplements is necessary, the costs of zinc supplements and ORS should remain affordable to all those in need. Zinc decreases the severity of the diarrhea episode. This should decrease the need for hospitalization and additional treatment, both of which can be extremely expensive for families. In addition, zinc should be encouraged instead of unnecessary and expensive antibiotics.

Zinc supplements have been procured from Nutriset for research studies and programs for \$0.14–0.31 per blister pack depending on volume. Zinc is inexpensive to produce, and technology transfer is being offered at rates affordable to pharmaceutical companies in developing countries. Thus, zinc supplements can be expected to remain at this low cost for both national and international purchasers.

## **Conclusion**

There is abundant evidence to justify the widespread inclusion of zinc supplements for diarrhea treatment. The world must face the challenges to enable this to happen. The programmatic changes are simple and incorporating these into diarrhea control programs will have a lasting impact on child health. National and local level health decision makers are needed to contribute local knowledge to successfully design programs that will ensure the highest coverage possible. Revitalizing diarrhea control programs to include zinc supplementation and reinforce the importance of ORS use is a child health goal the world cannot afford to ignore. Urgent action is needed from governments, international aid agencies, and donors to accept this challenge and decrease childhood diarrhea deaths. 600 million children are waiting.

## Endnotes

- 1 Reduced osmolarity oral rehydration salts (ORS) formulation – Report from a meeting of experts jointly organized by UNICEF and WHO. WHO/CAH/01.22
- 2 WHO/UNICEF Joint Statement on the Clinical Management of Acute Diarrhoea. WHO/CAH/04.
- 3 Prasad et al. Biochemical studies of dwarfism, hypogonadism and anemia. *Arch Internal Med* 1963;111:407-28.
- 4 Brown KH et al. Assessment of the risk of zinc deficiency in populations. *Food and Nutrition Bulletin* 2004;25:S130-162.
- 5 Zinc Investigators' Collaborative Group. 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.
- 6 Zinc Investigators' Collaborative Group. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. *J Pediatr* 1999;135:689-97.
- 7 Jones G et al. How many child deaths can we prevent this year? *Lancet* 2003;362:65-71.
- 8 WHO/UNICEF Joint Statement on the Clinical Management of Acute Diarrhoea. WHO/CAH/04.