

Differential Community Response to Introduction of Zinc for Childhood Diarrhea and Combination Therapy for Malaria in Southern Mali^{1,2}

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Abstract

Developing effective, affordable, and sustainable delivery strategies for the isolated low-income populations that stand to gain the most from micronutrient interventions has proven difficult. We discuss our experience with implementation of zinc as treatment for diarrhea in children less than 5 y of age over the course of 3 operational research studies in rural Sikasso Region, Mali, West Africa. The initial formative research study highlighted how malaria affects perceptions of diarrhea and its causes and that malaria and diarrhea are not necessarily viewed as distinct conditions. The second-phase pilot introduction demonstrated that, in introducing zinc treatment in malaria-endemic regions, it is especially important that both community- and facility-level providers be trained to manage sick children presenting with multiple symptoms. The third-phase study on large-scale implementation detected that the experience with implementation of new treatments for malaria is distinct from that of diarrhea. To some extent zinc treatment is the solution to a problem that communities may not recognize at all. Interventions to improve case management of sick children must be integrated across diseases and nutritional problems at both the facility and community levels. Operational research can identify points where integration should occur and how it should be carried out. Programs targeting single diseases or single nutritional problems can have a variety of deleterious effects on health systems, no matter how well they are planned. *J. Nutr.* 138: 642–645, 2008.

Background

Micronutrient deficiencies are widely recognized as a major contributor to under-5 mortality in low- and middle-income countries. Developing effective, affordable, and sustainable delivery strategies for isolated low-income populations that stand to gain the most from micronutrient interventions has proven difficult. In higher-income countries, food fortification has been a major channel for delivering these nutrients to populations. In low-income rural populations that obtain very little of their food from commercial sources, food fortification may have a limited impact. Daily or weekly supplementation is possible but presents a series of financial, logistical, and

behavioral challenges. To carry out such a program, governments must allocate sufficient funding in their budgets for this recurrent cost, large quantities of supplements need to be purchased, and then programs must mount effective behavior change interventions to convince populations to take the supplements on a regular basis.

In this article, we discuss experience with implementation of an alternative approach, micronutrients as treatment for acute infectious diseases, in this case zinc as treatment for diarrhea in children less than 5 y of age. Over the course of 3 operational research studies in rural Sikasso Region, Mali, West Africa, a 14-d course of dispersible zinc tablets, 20 mg/d for children 6 to 59 mo of age and 10 mg/d for children less than 6 mo, has been introduced as standard treatment for episodes of diarrhea along with oral rehydration solution. Meta-analysis of previous trials demonstrates that 10 to 14 d of zinc treatment is associated with decreased severity and duration of diarrhea, leading to decreased overall under-5 mortality (1). WHO and UNICEF currently recommend incorporating zinc into treatment of all young children with diarrhea, and that oral rehydration salts (ORS) be administered along with the zinc to prevent or treat dehydration (2).

In theory, this approach presents the following advantages. First, it provides supplementation to a group of people, parents

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of sick children, who are actively searching for a treatment. Acceptability may be greater than with daily supplements; people may question the necessity of taking pills when they are not sick. Second, it targets zinc toward a segment of the population that is most likely to benefit from supplementation: young children with diarrhea who lose considerable amounts of zinc through the diarrhea (3,4). Third, it positions zinc to replace other inappropriate treatments often used for the treatment of diarrhea. Although uncomplicated diarrhea is most commonly of viral origin, administration of antibiotics and antiparasitics to children with diarrhea is a global phenomenon (5). This contraindicated use of antibiotics not only promotes antimicrobial resistance (5) but also diverts scarce household resources to ineffective treatments and exposes children unnecessarily to antibiotics such as tetracycline that are not recommended for young children. One key reason for promoting zinc treatment for diarrhea is to decrease the inappropriate use of antibiotics to treat diarrhea, an effect of promotion of zinc treatment first documented in a trial in Bangladesh (6).

An obvious focus for the development of the content of interventions to promote zinc treatment for diarrhea includes local perceptions and treatment practices for diarrhea. We need an understanding of how diarrheal illness is perceived, under what conditions care is sought, what treatments are administered, and why it should be possible to develop an effective plan for zinc introduction. This focus was the initial plan for this series of studies, but results of the operational research demonstrated that the high incidence of malaria in the study sites affected all aspects of implementation. In this article we argue that in planning interventions to promote micronutrients as treatments for acute infectious diseases such as diarrhea or pneumonia (7), program planners must consider how other prevalent conditions such as malaria may affect demand for treatment, patterns of careseeking, and provider behavior.

Operational research on zinc treatment for diarrhea in Mali

The 3 phases of operational research were conducted in Bougouni District, Sikasso Region, in the southwestern part of Mali, West Africa. Dispersible zinc tablets and other treatments are distributed through community health centers and a village drug kit system. The kits are wooden cabinets stocked with 8 products including antimalarial drugs and ORS and are maintained by a community health worker (CHW). In the first phase of research, formative research to design the content of the strategy for zinc introduction was conducted in 2 health zones from July through December 2003 (8). This included in-depth interviews with parents of children experiencing diarrhea as well as semistructured interviews with parents, CHW, nurses in health centers, and traditional healers to explore local terminology, household practices and decision-making processes, treatment options, and sources of care. From information gathered in these interviews, messages and counseling materials aimed at promoting zinc were created, tested, and refined (8).

In the second phase, zinc treatment was introduced on a small scale in 2 health zones in 2004, with no comparison groups, to identify problems with the service delivery strategy in need of modification before large-scale implementation (P. J. Winch, K. E. Gilroy, S. Doumbia, A. E. Patterson, Z. Daou, A. Diawara, E. Swedberg, R. E. Black, and O. Fontaine, unpublished data). Changes in key indicators were assessed through baseline and final surveys conducted 6 mo apart. Operational issues associated with implementation were assessed through qualitative interviewing with health workers, CHW, and parents as well as

through routine monitoring of data (P. J. Winch, K. E. Gilroy, S. Doumbia, A. E. Patterson, Z. Daou, A. Diawara, E. Swedberg, R. E. Black, and O. Fontaine, unpublished data). Follow-up interviews in the home were conducted for a sample of 124 children receiving zinc treatment to assess the prevalence of possible side effects from the zinc treatment, compliance with a full course of zinc treatment, and changes in patterns of management of sick children resulting from introduction of zinc treatment (9).

The third phase from 2005 to 2007 was a large-scale study of the effect of zinc introduction on health systems, knowledge, and practices including treatment of diarrhea with zinc and ORS, and avoidance of antibiotics for uncomplicated cases of diarrhea. Two service delivery strategies were evaluated in 6 health zones each: zinc introduction through health centers only versus zinc introduction through health centers and village drug kits. Results for this latter study will be available in early 2008, but selected results from process documentation and monitoring are mentioned here.

Formative phase: perceptions of diarrhea and malaria

Public health and nutrition interventions must aim for high coverage to have an impact. When coverage is low, exposure to interventions may be limited to groups with higher levels of income and education who stand to benefit much less from the interventions (10). For zinc treatment of diarrhea, high coverage requires families to recognize episodes of diarrhea, label the episode as illnesses in need of treatment, and then decide to seek care outside the home from a provider who prescribes or sells zinc treatment for diarrhea. All of these factors were examined in the formative research phase (8).

Parents reported in the baseline survey for the second phase (unprompted) that most cases of simple diarrhea were either caused by teething (50%) or provoked by an episode of "malaria" (*sumaya*) (43%). Other causes of diarrhea were occasionally cited, such as transmission through breast milk (13%), inappropriate foods (26%), or unclean water (22%). Because teething is a normal developmental process and nothing can be done to "cure" a child of teething, many parents therefore believed that nothing effective could be done to alleviate a child's diarrhea. Because diarrhea is often accompanied by a fever, many parents also believe that *sumaya* is the ultimate cause of the illness. Intensive national and nongovernmental organization efforts in Mali have focused on raising awareness about the signs and treatment of malaria, and many people immediately identify and treat any illness characterized by a fever as malaria.

Malaria was clearly seen as a condition best treated with modern medicines. Care was rarely sought from the drug kits for children with diarrhea, as many parents felt that no real "treatment" was available, only ORS sachets, which were not perceived as being an effective stand-alone cure for diarrhea. Also, when diarrhea is accompanied with a fever, drug kit managers and community health center personnel routinely prescribe chloroquine to combat the presumed case of malaria.

Regardless of the cause of the diarrhea, treatment of diarrhea typically begins in the home with traditional medicines (*bama-nafura*) and/or antibiotics. Antibiotics were generally obtained from ambulatory or market vendors, and pills can be purchased individually or a few at a time to minimize the cost (less than US\$0.03 each). Tetracycline (*kumbleri*) is the most common antibiotic available from market vendors used to treat diarrhea. These results were confirmed in the baseline survey for the second phase (pilot study), which showed that only 11% of children received any ORS therapy during their episode of diarrhea (50%

obtained from health center, 24% from drug kit), and over 60% of cases of diarrhea were treated with an antibiotic (25% from health center, 75% from market).

Based on these findings from the formative phase, materials for training health workers and communication materials were created that focused on diarrhea, its causes, prevention, and recommended treatments including zinc and oral rehydration solution.

Second phase: management of multiple symptoms

The second phase pilot introduction of zinc treatment in 2 health zones focused on behavior of health care providers assessing and treating sick children and changes in patterns of management of diarrhea in the home by families. The baseline survey for the second phase pilot introduction of zinc treatment in 2 health zones found that the majority of children sick during the previous 2 wk (75%) reported multiple symptoms during their illness episode, with fever as the most common symptom, and fever and diarrhea the most common combination. However, it was found that health workers at both the facility and community levels were inadequately prepared for the management of children with multiple symptoms. Many CHW failed to integrate messages about diarrhea case management with information received in previous trainings on management of fever and other conditions. Rather than supplementing material from previous training courses, in many cases the new material on diarrhea management replaced previous information on management of fever, specifically for cases where the child presented with both diarrhea and fever in which the CHW followed the guidelines for diarrhea only when selecting treatments for the sick child. Through review of registers (notebooks) kept by the CHW and the household follow-up survey, it was found that 100% of children who presented with fever and diarrhea received zinc treatment, 61% received ORS, but only 8% received an antimalarial drug. Day-long meetings were held, in cooperation with the local health authorities, to discuss this issue in depth and to provide follow-up training to the CHW regarding children who present with fever and diarrhea.

Third phase: contrasting responses to introduction of new treatments for malaria and diarrhea

During the third phase of research (2006–2007), we gained further insight into factors affecting demand for zinc from the simultaneous implementation of an operational research study on the introduction of artemisinin combination therapy for malaria in young children. In both malaria and the zinc studies, a new treatment was being introduced for a common illness of children <5 y, and in both cases a course of treatment was sold for 100 francs CFA (US\$0.18). For the malaria study, there was an immediate and sustained increase in careseeking for fever from village drug kits from 120 to 229 visits/mo from September to November 2006 after the new malaria drug became available, at a time when careseeking normally is decreasing.

Meanwhile, in the zinc study, the increase in careseeking for diarrhea was slow (no overall change from May to November 2006). Intensive communication efforts beginning in November 2006 were necessary to increase careseeking for diarrhea. Further investigation of this situation revealed a series of differences in local perceptions of fever (presumed malaria) and diarrhea that shaped patterns of careseeking. Most of these differences had been noted in the initial formative research study, but this programmatic experience added valuable additional detail. Fever (malaria), known by the local term *sumaya*, is seen as a “real”

disease that can easily kill and will keep returning until a definitive treatment is administered. Diarrhea, especially at the time of teething, is seen as a normal step in the development of the child, not necessarily requiring treatment and, typically, not a fatal condition. Regarding available treatments, residents of the study areas are aware from announcements in the media that chloroquine is no longer effective, and there is considerable demand and expectation for a new malaria treatment. On the other hand, people perceive that there are multiple effective treatments for diarrhea including antibiotics (tetracycline), herbal remedies, and oral rehydration therapy and are not waiting or hoping for a new diarrhea treatment to be introduced.

In qualitative interviews with parents as part of the malaria study, it was found that diarrhea is often not considered a distinct condition from malaria. Parents associate diarrhea and vomiting with malaria and view the new malaria treatment as effective not only against fever but also against diarrhea and vomiting.

Most of the over 10 million deaths occurring in children under 5 y could be prevented if the delivery and utilization of interventions such as zinc treatment for diarrhea and effective anti-malarial drugs for malaria could be improved (11). This article summarizes the experience from operational research studies on the introduction of zinc treatment for diarrhea and how malaria affects the context for introduction of this intervention.

The initial formative research study highlighted how the presence of malaria affects perceptions of diarrhea and its causes, and that malaria and diarrhea are not necessarily viewed as distinct conditions. The second phase pilot introduction demonstrated that it is especially important in malaria-endemic regions that both the community- and facility-level providers need to be trained to manage sick children presenting with multiple symptoms, and frequently children will need to be treated for more than 1 condition. It is not sufficient to give training on management of diarrhea when introducing zinc treatment for diarrhea: training also needs to cover management of common combinations of presenting symptoms such as diarrhea and fever or diarrhea and cough. Training materials and registers/notebooks for recording symptoms and treatments should be designed knowing that many children will present with multiple symptoms.

The third phase study on large-scale implementation detected that the experience with implementation of new treatments for malaria is distinct from that of diarrhea and that careseeking shows greater increases in response to introduction of new malaria treatments, which communities perceive to be filling a gap created by drug resistance. To some extent zinc treatment is the solution to a problem that communities may not recognize at all.

In planning interventions to promote micronutrients as treatments for acute infectious diseases such as diarrhea or pneumonia (7), interventions to improve case management of sick children must be integrated across diseases and nutritional problems at both the facility and community levels (12). Operational research can identify points where integration should occur and how it should be carried out. Programs targeting single diseases or single nutritional problems can have a variety of deleterious effects on health systems, no matter how well they are planned (13).

Literature Cited

1. Bhutta ZA, Bird SM, Black RE, Brown KH, Gardner JM, Hidayat A, Khatun F, Martorell R, Ninh NX, 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.
2. WHO/UNICEF. Joint Statement: Clinical Management of Acute Diarrhoea, WHO/FCH/CAH/04.07 or UNICEF/PD/Diarrhoea/01. Geneva and New York: World Health Organization, Department of Child and Adolescent Health and Development, and United Nations Children's Fund, Programme Division; May 2004.
 3. Castillo-Duran C, Vial P, Uauy R. Trace mineral balance during acute diarrhea in infants. *J Pediatr.* 1988;113:452–7.
 4. Roy SK, Behrens RH, Haider R, Akramuzzaman SM, Mahalanabis D, Wahed MA, Tomkins AM. 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.
 5. Radyowijati A, Haak H. Improving antibiotic use in low-income countries: an overview of evidence on determinants. *Soc Sci Med.* 2003;57:733–44.
 6. Baqui AH, Black RE, El Arifeen S, Yunus M, Zaman K, Begum N, Roess AA, Santosham M. 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;22:440–2.
 7. Brooks WA, Yunus M, Santosham M, Wahed MA, Nahar K, Yeasmin S, Black RE. Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. *Lancet.* 2004;363:1683–8.
 8. Ellis AA, Winch P, Daou Z, Gilroy KE, Swedberg E. Home management of childhood diarrhoea in southern Mali—implications for the introduction of zinc treatment. *Soc Sci Med.* 2007;64:701–12.
 9. Winch PJ, Gilroy KE, Doumbia S, Patterson AE, Daou Z, Coulibaly S, Swedberg E, Black RE, Fontaine O. Prescription and administration of a 14-day regimen of zinc treatment for childhood diarrhea in Mali. *Am J Trop Med Hyg.* 2006;74:880–3.
 10. Habicht JP. Applying an equity lens to child health and mortality: more of the same is not enough. *Lancet.* 2003;362:233–41.
 11. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS. How many child deaths can we prevent this year? *Lancet.* 2003;362:65–71.
 12. Winch PJ, Leban K, Casazza L, Walker L, Percy K. An implementation framework for household and community integrated management of childhood illness. *Health Policy Plan.* 2002;17:345–53.
 13. Unger JP, De Paepe P, Green A. A code of best practice for disease control programmes to avoid damaging health care services in developing countries. *Int J Health Plann Manage.* 2003;18: Suppl 1:S27–39.