

Zinc and low osmolarity oral rehydration salts for diarrhoea: a renewed call to action

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Abstract In 2004, WHO and the United Nations Children's Fund (UNICEF) released a joint statement recommending a new lower osmolarity oral rehydration salts (ORS) formulation and zinc supplementation for diarrhoea management. More than 5 years later, diarrhoea remains the second leading cause of death and few children in developing countries are receiving these life-saving interventions. Many countries are stalled in the technicalities of adapting national policy, while others struggle to find the funds for start-up activities. For nearly all countries, zinc supplements for children are not available locally; thus, zinc procurement continues to be a major obstacle. Global resources have not been sufficient to bring diarrhoea management to the forefront; thus, the introduction of these new recommendations has remained slow. Revitalizing diarrhoea management must become an international priority if we are going to reduce the burden of diarrhoea deaths and overall child mortality around the world.

Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Diarrhoea remains a leading cause of death among infants and young children, accounting for 18% of child deaths and 13% of all disability-adjusted life years (DALYs).¹ If the United Nations Millennium Development Goal (MDG) 4 for reducing child mortality by two-thirds is to be met by 2015, greater attention must be given to reducing diarrhoea morbidity and mortality.² In May 2004, WHO and the United Nations Children's Fund (UNICEF) released a joint statement to decrease diarrhoea deaths among the world's most vulnerable children.³ This statement recommended two simple and inexpensive changes: i) the switch to a new lower osmolarity formulation for oral rehydration salts (ORS)⁴ that reduces the need for intravenous fluids and shortens the duration of the episode⁵; and ii) the introduction of zinc supplementation for 10–14 days, as an adjunct therapy that decreases the duration and severity of the episode and the likelihood of subsequent infections in the 2–3 months following treatment.^{4,6}

This joint recommendation came after scientific consensus and recognition that zinc and low osmolarity ORS were critical for the reduction of diarrhoea mortality. It is estimated that more than three quarters of all diarrhoea deaths could be prevented with full coverage and utilization of zinc and ORS.⁷ Support for these recommendations has also come from the 2008 Copenhagen Consensus, a group of leading global economists that ranked zinc supplementation as the most cost-effective intervention for advancing human development.⁸ Despite the evidence of benefit, there has been little progress on widespread introduction of low osmolarity ORS and zinc for diarrhoea treatment. Many countries have changed diarrhoea management policies to include low osmolarity ORS and zinc, but there is a gap between policy change and effective programme implementation with very

few children currently being appropriately treated. Although historically, few new health interventions have enjoyed expedited roll-out around the world, it is becoming more common, e.g. with new vaccines as greater attention is given to implementing proven interventions.

As the countdown to the year 2015 continues, median coverage rates for oral rehydration therapy (ORT) hover at 38% of episodes⁹ among the 68 UNICEF priority countries with an increase in use of only 2 percentage points reported from 2000 to 2006.¹⁰ The movement away from vertical programmes towards integrated case management of childhood infections has contributed to the shift from home and community-based management of diarrhoea to facility care and low levels of correct case management.¹⁰ The acceleration of these simple and effective child survival tools has fallen off the priority lists for global and national policy leaders and programme managers.

Initial global effort

Immediately after the release of the joint statement in 2004, key international agencies made efforts to help countries incorporate low osmolarity ORS and zinc in their child-health programmes. UNICEF issued a joint directive that provided all country offices with information regarding procurement and updated programme guidance. WHO also offered support to country offices, began updating all diarrhoea treatment guidelines and added zinc to the WHO Essential Medicines List. The United States Agency for International Development (USAID) began working with manufacturers to develop quality zinc products for international and national procurement.

In June 2004, an international meeting of child health and diarrhoea treatment experts was convened to identify the support that would be needed to ensure accelerated roll-out

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of low osmolarity ORS and zinc. The group recognized the need for global collaboration and country assistance and called for the formation of an international Zinc Task Force, a collaboration of Johns Hopkins University, the United Nations' agencies, USAID, bilateral organizations and researchers. With limited funding and an 18-month timetable, the Zinc Task Force focused on key problems affecting numerous countries and worked to address issues at global and regional levels. These included: (i) diarrhoea treatment policy at country level; (ii) lack of a global zinc supply; (iii) financing for initial zinc procurement and start-up activities; (iv) creating demand within countries and (v) needs for operational research, monitoring and evaluation. Though there have been advances in each of these areas, big challenges continue to impede programme advances. This paper examines the global and national efforts to date and identifies obstacles to the faster implementation in each of these five major areas.

National policy adaptation

As WHO and UNICEF released the joint recommendation, it was recognized that additional support would be needed at the global level to assist countries with implementation. Few country policy-makers were aware of the recommendations and even fewer knew the strong scientific evidence.

From 2006 to early 2007, six regional and two national diarrhoea management advocacy and training workshops were held for policy-makers, paediatricians and child-health experts from more than 50 countries. These workshops provided participants with focused training, including the rationale for policy change and an opportunity to discuss financial and implementation challenges. Published guidelines also provided detailed technical information for updating policy, implementing new ORS and zinc as part of diarrhoea management and child-survival strategies, managing the division between public versus private sectors, streamlining product and supply logistics, and monitoring and evaluation.¹¹

In the past 4 years, 66 and 46 countries have successfully changed national child-health policies to include

Box 1. Development of a Zinc Start-up and Procurement Fund (ZPF)

The introduction of zinc for the management of diarrhoea requires the procurement of zinc, the development of training materials and the training of multiple cadres of health-care professionals all of which can delay country roll-out. One possible solution is the creation of an international Zinc Procurement Fund (ZPF) to provide funds to countries to "bridge the gap" from the time the child-health policy is changed until zinc can be incorporated into the routine budget. The ZPF would assist countries with initial procurement and one time costs associated with the introduction of zinc. By having a funding mechanism available to support the initial roll-out activities, countries will be able to expedite the introduction of zinc and gain confidence with new changes while making the necessary budgetary adaptations to ensure sustainability.

Additionally, initial global investments in a centralized funding and procurement model, such as a ZPF, could be vital for the support of the scale-up in all countries, not just those which receive funds via targeted child survival activities. In an effort to maintain low costs, a ZPF initiative could be implemented by UNICEF as an integrated part of its child-survival programme. Overall, a ZPF has the potential to expedite the widespread availability of zinc especially among countries where initial zinc supplies and costs are creating prohibitive obstacles.

low osmolarity ORS and zinc, respectively. For many countries, the support from professional organizations such as national paediatric associations or the leadership of an opinion leader as a national champion were critical to the successful policy process. In addition, the cooperation from private sector manufacturers has also been helpful, especially in countries that place emphasis on locally-produced products.

For many countries, adopting a child-health policy is complex and involves several national ministries. Because zinc supplements were initially not produced locally in any country, the registration and importation of this product required additional input from drug regulatory agencies and procurement officials at country level. As questions arose from the various ministries throughout the policy process, countries did not have the technical assistance on hand to keep the process moving smoothly, resulting in lengthy delays or the cessation of the process.¹² For other countries, the policy adaptation process has been simple, but country officials are hesitant to move forward until a country implementation plan is in place and the funding is secured. These obstacles still stand in the way of introducing zinc and low osmolarity ORS in more than half of the 68 UNICEF priority countries.

Global supply

The 2004 WHO/UNICEF recommendations rely on the widespread availability of two commodities. While ORS has been available for many years, the switch to low osmolarity ORS has been challenging for some countries.

ORS is manufactured locally or imported from a regional or international supplier, including UNICEF. Although UNICEF suppliers were mandated to make a transition to the lower osmolarity formulation, local and regional suppliers have been slower to adjust their manufacturing practices. Many countries have had to pass national regulations to force local and regional manufacturers to adjust the formulation.¹³ For many countries, the drop in demand over the years has also resulted in decreased production and an inefficient supply chain for ORS, which will need to be corrected if distribution is to cover all geographic and socioeconomic sectors of each country.

Prior to the inclusion of zinc in the diarrhoea management recommendations, supplements with zinc specifically suitable for children were not on the market in any country. These must be dispersible tablets or syrup and should not contain other micronutrients that may compete for absorption, as outlined in WHO manufacturing guidelines.¹¹ In 2004, manufacturers had developed zinc products only for use in research studies, and no manufacturer could meet WHO's Good Manufacturing Practices (GMP) criteria for international procurement via UNICEF or WHO. After zinc was added to the WHO Essential Medicines List in 2005, countries were able to include it in national medicines lists and as part of national health budgets. UNICEF has been supplying 20 mg dispersible zinc tablets since 2006 from two suppliers. Though it is expected that additional companies will introduce quality products in 2009,

quality, age-appropriate zinc formulations remain limited. Thus UNICEF, USAID and WHO must continue to assist new suppliers for international procurement.

Locally produced zinc products, that may or not meet the GMP standards for international procurement, are now available in Bangladesh, Egypt, El Salvador, India, Indonesia, Nepal, Pakistan and the United Republic of Tanzania. Although some manufacturers initially relied on technology transfer, many companies are able to develop a product with minor technical support. Additional support may be available soon from WHO as zinc is now formally part of the WHO prequalification programme, which will set aside funds to assist manufacturers with the development of quality products. For many countries, local manufacturers have not yet considered the possibility of manufacturing zinc and will not do so until their national government changes policy. This can slow the pace of implementation drastically because many governments are hesitant to change national policy without locally manufactured product.

It is critical to increase the number of manufacturers for both international and national markets. Competition will reduce prices over time and ensure an adequate supply as demand increases. In addition, the private sector involvement in many countries can create opportunities to reach carers who visit local shops, pharmacies, or private physicians as a first-line treatment for their child with diarrhoea. Continued technical support from the international community will be critical in the next few years to ensure that local manufacturers emerge with quality products¹¹ endorsed by the national government and eligible for procurement from other countries in the region.

Financing

The switch from the original ORS formulation to low osmolarity ORS does not require additional programme funds with regard to the manufacturing procedures. The product is more efficacious and is 17% cheaper because it requires less salt and glucose and thus less packaging. The introduction of zinc, however, requires the addition of zinc procurement to the budget. For many countries, finding funds required

Box 2. Promotion of ORS in the early 1980s

In the 1980s, diarrhoeal diseases control activities were a priority for WHO and UNICEF and most other bilateral organizations and nongovernmental organizations (NGOs). Significant funds were made available for training, supervision, production of ORS, evaluation and especially for communication. The communication strategies were carefully developed, with mass media and market research, culturally relevant use of media and integration of sociological and anthropological research findings into the media messages.

In the mid-1990s, communication strategies for the promotion of ORS were stopped in most countries due to competing priorities and this resulted in a stagnation or decrease in ORS use rates.

ORS, oral rehydration salts.

for initial start-up activities to introduce zinc and increase coverage of both ORS and zinc throughout the country is challenging. Regular training for health-care providers may not occur at the time when zinc is introduced so the country must conduct additional training that can be expensive and logistically challenging. Although revisions have been made to training manuals supplied from WHO, each country must handle its own local adaptations and the development of local language editions, which can be expensive and time consuming. Although zinc is inexpensive and cost-effective,¹⁴ there is still need for additional start-up funds, which could be addressed by a special fund set up for this purpose (Box 1).

Training of health-care workers

Quality training has the potential to accelerate uptake, ensure zinc is used correctly, increase ORS use, decrease unnecessary antibiotic use, increase referral and thus decrease morbidity and mortality. Low osmolarity ORS and zinc are now included in all of the WHO training guidelines and recommendations for the treatment of diarrhoea, although local adaptations and translations are not widespread.¹⁵

Training and retraining is a vast undertaking that involves multiple tiers of health-care workers including a large cadre of community-health providers. Where the private sector provides a large portion of the health care, partnering with local producers of zinc and/or ORS may be critical to achieve the training needs among private health professionals.

A more difficult issue arises when governments begin to consider how to train the non-formal health sector

including those with little to no medical training. In Uttar Pradesh, India, the POUZN (Point-of-Use Water Disinfection and Zinc Treatment) project uses local NGO staff to train the non-formal sector in proper diarrhoea management through "grassroots medical representatives" (C Saade, personal communication, 2008). Demonstration projects to explore the effectiveness of additional innovative strategies such as incentive programmes to increase motivation are needed. Because country roll-out is occurring slowly, there are few documented lessons to which other countries can look for assistance and support with regard to this critical challenge. The resistance to involve this sector is strong in many countries and may require additional technical support or outside funds to pilot and evaluate innovative approaches.

Creating demand

Zinc and low osmolarity ORS have been shown to be acceptable to both children and caregivers.¹⁶ Effectiveness studies in Bangladesh, India, Mali and Pakistan have demonstrated that community-based programmes increase the use of zinc and the introduction of zinc increases ORS use in the same communities.^{6,17,18} (P Winch and Z Bhutta, personal communication, 2008). A formative research tool is now available for the development of locally appropriate messages for the promotion of low osmolarity ORS and zinc.¹⁹ Successful message development by targeted projects such as the SUZY (Scaling Up Zinc for Young children) project in Bangladesh (S Kaiser, personal communication, 2008) and the USAID/PSI Diarrhoea Treatment Kit project in Pursat and Siem Reap (Cambodia) has led to an increased demand for zinc and low osmolarity ORS in the targeted areas.¹⁹

Table 1. Countries^a with zinc and low osmolarity ORS available via pilot programming or via routine public and private sector outlets

Country	Formative/ Pilot ^b	Public Sector Product ^c	Private Sector Product ^c
UNICEF priority countries (2008)			
Afghanistan			
Angola	Yes		
Azerbaijan			
Bangladesh	Yes	Yes	Yes
Benin	Yes	Yes	Yes
Bolivia (Plurinational State of)	Yes	Yes	Yes
Botswana			
Brazil			
Burkina Faso			
Burundi			
Cambodia	Yes		Yes
Cameroon	Yes		
Central African Republic			
Chad		Yes	
China			
Congo			
Côte d'Ivoire			
Democratic People's Republic of Korea			
Democratic Republic of the Congo	Yes	Yes	
Djibouti			
Egypt	Yes		Yes
Equatorial Guinea			
Eritrea	Yes		
Ethiopia			
Gabon			
Gambia			
Ghana			
Guatemala	Yes	Yes	
Guinea			
Guinea-Bissau			
Haiti			
India	Yes	Yes	Yes
Indonesia	Yes	Yes	Yes
Iraq			
Kenya		Yes	
Lao People's Democratic Republic			
Lesotho		Yes	
Liberia			
Madagascar	Yes	Yes	
Malawi			
Mali	Yes		
Mauritania			
Mexico			
Morocco			
Mozambique	Yes		
Myanmar	Yes		
Nepal	Yes	Yes	Yes
Niger	Yes		
Nigeria	Yes	Yes	
Pakistan	Yes		Yes
Papua New Guinea			
Peru	Yes		
Philippines	Yes		
Rwanda	Yes		

(Table 1, cont.)

Country	Formative/ Pilot ^b	Public Sector Product ^c	Private Sector Product ^c
Senegal	Yes	Yes	
Sierra Leone	Yes		
Somalia			
South Africa			
Sudan	Yes		
Swaziland			
Tajikistan			
Togo			
Turkmenistan			
Uganda			
United Republic of Tanzania	Yes		Yes
Yemen			
Zambia	Yes		
Zimbabwe			
Other countries taking steps to introduce zinc			
El Salvador		Yes	
Kazakhstan	Yes		
Nicaragua		Yes	

ORS, oral rehydration salts.

^a All UNICEF priority countries are included. Additional countries included if they are taking steps to introduce zinc either via formative research/pilot interventions or introduction in the private or public sector.

^b Formative/pilot includes any formative research activities or pilot intervention programmes conducted in the country.

^c Product availability denotes any available product and does not include a coverage minimum. Most countries had very minimal coverage as of 2009.

In countries where ORS use rates are high, such as Bangladesh, zinc should be added to current ORS public and private sector promotion schemes. Where ORS use rates are low, such as in Burkina Faso and Mali, the promotion of zinc and ORS together is critical and may include social marketing, expansion of private sector markets and targeted behavioural change campaigns. Although the promotion of ORS was tremendously successful in the early and mid-1980s (Box 2), current strategies employed by many countries are in desperate need of revitalization.

Providing low osmolarity ORS and zinc only through public sector clinics is not a comprehensive and lasting strategy that has been effective in any country. The revitalization of community-health workers with reach into the least fortunate communities will be critical to achieving targeted coverage rates. In addition, incorporating the private sector, the medical and non-medical, formal and informal sectors, may help reach additional segments of the population. In a recent large-scale effectiveness study in rural Mali, where the local health clinics were the sole providers of zinc and low osmolarity ORS, only 19% of the diarrhoea episodes were reached. However,

when the intervention was rolled out throughout the community via the village health workers, coverage increased to 43% (P Winch, personal communication, 2008). It may also be effective to utilize private sector health workers and pharmaceutical representatives as trainers, promoters and prescribers. For many countries, the lack of funds and technical assistance to conduct the formative work needed to develop a fresh approach to diarrhoea management can be a limitation. A practical and systematic tool has been developed by the BASICS project (available at: <http://www.basics.org>) to engage country-level implementers in the process of determining the best way to introduce low osmolarity ORS and zinc.

Countries need to be able to project early zinc demand to determine initial national procurement and strengthen the supply chain to ensure supplies reach the most peripheral parts of the health-care delivery system. It is critical that agencies continue to help countries understand the evidence supporting community case management of diarrhoea and the expected increase in demand of both low osmolarity ORS and zinc if coupled with a successful training and promotion strategy.

Continued research

It is widely recognized that introducing zinc and increasing the dismal coverage rates for ORS will take additional research to identify the most effective delivery strategies to ensure these treatments reach the poorest of the poor – those who are often the last to receive services. No studies have been conducted comparing alternative delivery strategies in the public sector on ORS and zinc uptake so there are few concrete examples around which countries can build programmes. Additional operations research studies in several key countries would provide the critical information needed to help programme managers design efficient intervention programmes so as to improve upon the current method of inserting zinc into a failing system, achieving only minimal impact.

Monitoring and evaluation of new strategies is also critical yet little is being done to ensure this happens. New Demographic and Health Surveys and Multiple Indicator Cluster Surveys will include questions to ascertain current zinc coverage rates, but results are reported only every 3–5 years and may not be large enough to reflect coverage in administrative units, such as

districts, where implementation and oversight are controlled.

Where do we go from here?

Low osmolarity ORS and zinc are inexpensive, safe and easy to use and have the potential to dramatically lower diarrhoea morbidity and mortality. In Bangladesh and India, large-scale programmes have demonstrated that together they can decrease unnecessary use of antibiotics, reinvigorate community management of diarrhoea while keeping costs low and treatment acceptable to both children and caregivers and, most importantly, save lives.^{6,18} Five years after the call for action in 2004, only 29 countries have begun to explore the possibility of introducing low osmolarity ORS and zinc via formative research or pilot programmes and only 22 countries have zinc available in either the private or public sectors (Table 1).

Even for countries that have achieved success in early introduction, coverage is extremely limited.

Why is there so little progress in implementing these life-saving interventions? Why do we have two promising treatments, yet no global action plan or dedicated funding? Although child-survival funding increased by 63% from 2003 to 2006, funding for key strategies for diarrhoea management such as the Integrated Management of Childhood Illnesses decreased by 59% during that same period.²⁰ Diarrhoea continues to kill nearly 2 million children each year, leads to millions of hospitalizations and contributes to long-term nutritional consequences.²¹ It has been 5 years since the release of the WHO/UNICEF joint statement and, although some progress has been made, the small number of children who have access to these interventions represents an extremely small proportion of those who are in

need. Because the treatments we have available today are safe, effective and inexpensive, community-based diarrhoea management should be a top global health priority. In the past 5 years, international meetings have convened and verbal commitments have been made by funders and international agencies alike, but the necessary funding has not been forthcoming. If MDG 4 is to be met by 2015, the prevention and treatment of diarrhoea must become an international priority. ■

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Résumé

Supplémentation en zinc et sels de réhydratation orale à faible osmolarité contre la diarrhée : encore une fois, il faut agir !

En 2004, l'OMS et le Fonds des Nations Unies pour l'enfance (UNICEF) ont émis une déclaration conjointe recommandant une nouvelle formulation de sels de réhydratation orale (SRO) à plus faible osmolarité et une supplémentation en zinc pour la prise en charge des diarrhées. Plus de 5 ans après, les diarrhées restent la deuxième cause de décès et peu d'enfants dans les pays en développement bénéficient de ces interventions, capables de sauver des vies. De nombreux pays sont bloqués par des détails techniques dans l'adaptation de leur politique nationale, tandis que d'autres luttent pour trouver des sources de financement

pour les opérations de lancement. Dans leur quasi-totalité, les pays ne disposent pas localement de suppléments pédiatriques en zinc ; se procurer ces suppléments demeure donc un obstacle majeur. Les ressources mondiales n'ont pas suffi pour faire passer la prise en charge des diarrhées au premier plan des interventions. Ainsi, l'introduction de ces nouvelles recommandations est restée lente. Donner un nouvel élan à la prise en charge des diarrhées doit devenir une priorité internationale si l'on veut réduire la charge de mortalité due à ces maladies et la mortalité infantile globale partout dans le monde.

Resumen

Zinc y sales de rehidratación oral de baja osmolaridad contra la diarrea: nuevo llamamiento a la acción

En 2004, la OMS y el Fondo de las Naciones Unidas para la Infancia (UNICEF) difundieron una declaración conjunta en la que recomendaban una nueva preparación de sales de rehidratación oral (SRO) de baja osmolaridad y suplementos de zinc como tratamiento de la diarrea. Más de cinco años después, la diarrea sigue siendo la segunda causa de muerte, y en los países en desarrollo son muy pocos los niños que se benefician de esas intervenciones que salvan vidas. Muchos países están paralizados debatiendo detalles técnicos para adaptar su política nacional, mientras otros intentan con dificultad encontrar los fondos necesarios para iniciar

sus actividades. En casi todos los países, no es posible encontrar localmente suplementos de zinc para la población infantil, y esos problemas para adquirir zinc siguen siendo un gran obstáculo. Los recursos mundiales no han sido suficientes para resaltar la importancia del tratamiento de la diarrea, de ahí la lentitud en la aplicación de las nuevas recomendaciones. La reactivación del tratamiento de la diarrea debe constituir una prioridad internacional si deseamos reducir la carga de mortalidad a ella asociada y la mortalidad general en la niñez en todo el mundo.

ملخص

الزنج وأملاح الإمهاء الفموية المنخفضة الأسمولية لمعالجة الإسهال: دعوة متجددة للعمل

الأنشطة. وبالنسبة لجميع البلدان تقريباً لا تتوافر الكميات التكميلية من الزنج في المواقع المحلية، مما يجعل شراء الزنج يمثل عبءاً رئيسية. والموارد العالمية غير كافية لجعل معالجة الإسهال تحتل موقعاً متقدماً، وبالتالي فإن إدخال هذه التوصيات الجديدة ظل بطيئاً. وينبغي أن يمثل إحياء المعالجة المحدثة للإسهال واحدة من الأولويات الدولية إذا ما أردنا خفض عبء الوفيات من الإسهال ومن تمّ مجمل وفيات الأطفال في جميع أرجاء العالم.

في عام 2004، أطلقت منظمة الصحة العالمية واليونيسف بياناً مشتركاً يوصي بصيغة جديدة لأملاح إمهاء ذات أسمولية أقل مع كميات تكميلية من الزنج لمعالجة الإسهال. وبعد مرور ما يزيد على 5 سنوات، لا يزال الإسهال يمثل السبب الثاني الأكثر أهمية للوفيات، كما أن عدداً قليلاً من الأطفال في البلدان النامية يتلقون هذه التدخلات المنقذة للحياة. وهناك العديد من البلدان المتأخرة في المجالات التقنية المتعلقة بتكثيف السياسات الوطنية، فيما تواجه بلدان أخرى صعوبة كبيرة للحصول على التمويل للبدء بهذه

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