

Implementing the New Recommendations on the Clinical Management of Diarrhoea

Guidelines for Policy Makers and Programme Managers



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Introduction

1

Acute diarrhoea remains a leading cause of childhood deaths – despite the undeniable success of oral rehydration therapy (ORT) over the years. Since 1978, when the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) adopted ORT using oral rehydration salts (ORS) solution as the primary tool to fight dehydration, the mortality rate for children under the age of five suffering from acute diarrhoea has fallen from 4.5 million to 1.8 million deaths annually. However, in spite of this impressive achievement, acute diarrhoea remains a leading cause of death among children in developing countries.

WHO and UNICEF have released revised recommendations aimed at dramatically cutting the number of deaths due to diarrhoea. These new recommendations take into account two significant recent advances: demonstration of the increased efficacy of a new formulation for ORS containing lower concentrations of glucose and salt, and success in using zinc supplementation in addition to rehydration therapy in the management of diarrhoeal diseases. Prevention and treatment of dehydration with ORS and fluid commonly available at home, breastfeeding, continued feeding, selective use of antibiotics, and providing zinc supplementation for 10 to 14 days are the critical therapies that will help us achieve these goals.

This manual provides policy makers and programme managers with the information they need to introduce and/or scale up a national decision to introduce the new ORS formulation and zinc supplementation as part of the clinical management of diarrhoeal diseases.

2

New recommendations on the clinical management of diarrhoea

The overall goals of this section are —

- To create a good understanding about the new recommendations made by WHO and UNICEF for the clinical management of diarrhoea
- To enable decision-makers in the health sector to make an informed choice on the adoption/introduction of these new recommendations

2.1 What are the new recommendations?

Health care workers treating children for diarrhoea should be using the new low osmolarity ORS solution recommended by WHO and UNICEF in 2003. As before, they are encouraged to provide caretakers of children with diarrhoea with two 1-litre packets of the new ORS solution for home use until the diarrhoea stops.

Caretakers should also be provided with enough zinc supplements to continue home treatment for 10-14 days. Printed material (including text and illustrations) with advice on preventing and treating diarrhoea at home should accompany the ORS and zinc supplements.

Use of home fluids for preventing dehydration is still recommended, and the criteria for the selection of an appropriate home fluid remains unchanged. However, children with diarrhoea treated at home with home-based fluids should also receive zinc supplements for 10-14 days.

Success in reducing death and illness due to diarrhoea depends on acceptance of the scientific basis and benefits of these new therapies by governments and medical communities. It also depends on reinforcing family knowledge of prevention and treatment of diarrhoea, and providing information and support to underserved families.

Therefore, the revised recommendations emphasize family and community understanding of how to manage diarrhoea.

- Mothers and other caregivers should —
 - Prevent dehydration through the early administration of increased amounts of appropriate fluids available in the home, including ORS solution, if on hand
 - Continue feeding (or increase breastfeeding) during the episode and increase feeding afterward
 - Recognize the signs of dehydration and take the child to a health care provider for new ORS or intravenous electrolyte solution, and familiarize themselves with symptoms requiring medical treatment (e.g. bloody diarrhoea)
 - Provide children with 20 mg per day of zinc supplementation for 10-14 days (10 mg per day for infants under the age of six months)

-
- Health care workers should —
 - Counsel mothers to begin administering suitable available home fluids immediately upon onset of diarrhoea in a child
 - Treat dehydration with new ORS solution (or with an intravenous electrolyte solution in cases of severe dehydration)
 - Emphasize continued feeding or increased breastfeeding during, and increased feeding after, the diarrhoeal episode
 - Use antibiotics only when appropriate, i.e., in the presence of bloody diarrhoea or shigellosis, and abstain from administering anti-diarrhoeal drugs
 - Provide children with 20 mg per day of zinc supplementation for 10-14 days (10 mg per day for infants under six months old)
 - Advise mothers of the need to increase fluids and continue feeding during future diarrhoeal episodes

2.2 The scientific evidence supporting these new recommendations

The revised recommendations formulated by WHO and UNICEF, in collaboration with the United States Agency for International Development (USAID) and other experts worldwide, are based on elements of past recommendations (early administration of increased amount of fluids, continued feeding or increased breastfeeding, and recognition of signs of dehydration), and take into account two recent significant research findings.

- Development of an improved formula for ORS solution with reduced levels of glucose and salt (NaCl) that shortens the duration of diarrhoea, reduces stool volume and reduces the need for unscheduled intravenous (IV) fluids
- Demonstration that zinc supplements given during and just after an episode of acute diarrhoea reduce the duration and severity of the episode, and lower the incidence of diarrhoea in the following 2-3 months

2.2.1 Improved ORS formulation

For more than 25 years, WHO and UNICEF have recommended a single formulation of glucose-based ORS to prevent or treat dehydration from diarrhoea regardless of cause or age group affected. The ORS recommended until recently, which provides a solution containing 90 mEq/l of sodium with a total osmolarity of 311 mOsm/l, has proven effective and without apparent adverse effects in worldwide use. It has contributed substantially to the dramatic global reduction in mortality from diarrhoeal disease during the period.

For the past 20 years, numerous studies have been undertaken to develop an “improved” ORS. The goal was a product that would be at least as safe and effective as standard ORS for preventing or treating dehydration but would also reduce stool output or have other important clinical benefits. One approach has consisted in reducing the osmolarity of ORS solution to avoid possible adverse effects of hypertonicity on net fluid absorption. This was done by reducing the solution’s glucose and salt (NaCl) concentrations.

Studies to evaluate this approach were reviewed at a consultative technical meeting held in New York (USA) in July 2001. Technical recommendations were made to WHO and UNICEF on the efficacy and safety of reduced osmolarity ORS in children with acute non-cholera diarrhoea, and in adults and children with cholera.

These studies showed that the efficacy of ORS solution for treating children with acute non-cholera diarrhoea is improved by reducing its sodium concentration to 75 mEq/l, its glucose concentration to 75 mmol/l and its total osmolarity to 245 mOsm/l. The need for unscheduled supplemental IV therapy in children given this solution was reduced by 33%. In a combined analysis of this study and studies with other reduced osmolarity ORS solutions (osmolarity 210-268 mOsm/l, sodium 50-75 mEq/l) stool output was also reduced by about 20% and the incidence of vomiting by about 30%. The 245 mOsm/l solution also appeared to be as safe and at least as effective as standard ORS for use in children with cholera.

The reduced osmolarity ORS containing 75 mEq/l sodium, 75 mmol/l glucose (total osmolarity of 245 mOsm/l) is as effective as standard ORS in adults with cholera, and therefore can be used in place of standard ORS for treating adults with cholera.

Because of the improved effectiveness of reduced osmolarity ORS solution, especially for children with acute, non-cholera diarrhoea, WHO and UNICEF now recommend that countries use and manufacture the following formulation in place of the previously recommended ORS solution with a total osmolarity of 311 mOsm/l.

Reduced osmolarity ORS	grams/litre	Reduced osmolarity ORS	mmol/litre
Sodium chloride	2.6	Sodium	75
Glucose, anhydrous	13.5	Chloride	65
Potassium chloride	1.5	Glucose, anhydrous	75
Trisodium citrate, dehydrate	2.9	Potassium	20
		Citrate	10
Total osmolarity			245

Although this single ORS formulation is recommended, WHO and UNICEF have previously published criteria that remain unchanged for acceptable ORS formulations. These criteria are listed below; they specify the desired characteristics of the solution after it has been prepared according to the instructions on the packet.

- The total substance concentration (including that contributed by glucose) should be within the range of 200–310 mmol/l
- The individual substance concentration
 - Glucose — Should at least equal that of sodium but should not exceed 111 mmol/l
 - Sodium — Should be within the range of 60-90 mEq/l
 - Potassium — Should be within the range of 15-25 mEq/l
 - Citrate — Should be within the range of 8-12 mmol/l
 - Chloride — Should be within the range of 50-80 mEq/l

2.2.2 Zinc supplement in the treatment of acute diarrhoea

The use of zinc in treating acute diarrhoea is thought to affect immune function or intestinal structure or function, and the epithelial recovery process during diarrhoea. Zinc deficiency has been found to be widespread among children in developing countries, and occurs in most of Latin America, Africa, the Middle East and South Asia. Zinc has been identified to play a critical role in

metallo-enzymes, polyribosomes, the cell membrane and cellular function, leading to the belief that it also plays a central role in cellular growth and in the function of the immune system. It has also been shown that intestinal zinc losses during diarrhoea aggravate pre-existing zinc deficiency.

Convincing evidence for the clinical importance of zinc has come from randomised controlled trials evaluating the impact of zinc supplementation during acute and persistent diarrhoea. In 2001, WHO convened a meeting of experts in New Delhi, India, to review the results of all these studies.

The main features of these trials include randomised placebo-controlled design, subjects aged between one month and five years, and daily elemental zinc dose ranging from 5 to 45 mg per day. In these trials, children receiving zinc had a significantly faster recovery than children receiving placebo (about 20% reduction in the duration of diarrhoea). Zinc treatment also resulted in a 20% reduction in the risk of acute episodes to last more than seven days. Some of these studies were hospital-based, and measured impact of zinc supplementation on stool output. Reduction in total stool output ranged from 18% to 59% in the zinc-treated children when compared to the placebo group. In all these studies, the effect of zinc did not vary significantly with age or nutritional status assessed by anthropometry. The effects were not dependent upon the type of zinc salts used as zinc sulphate, zinc acetate or zinc gluconate were equally effective. Although the optimal dose is yet to be determined, there seems to be little gain in efficacy when the commonly used 20 mg daily dose of elemental zinc is increased to 30-40 mg daily. Although a majority of the studies so far were conducted in south-east Asia where zinc deficiency is common, studies conducted in other parts of the world showed similar results.

The experts concluded that zinc supplementation, given at a dose of 10–20 mg per day for 10–14 days, is efficacious in significantly reducing severity of diarrhoea and duration of the episode.

A summary of the scientific evidence justifying the new diarrhoea management recommendations can be found in Annex I. All the articles that have been used to prepare this summary, together with some important reference materials and sample presentations in PowerPoint format to facilitate advocacy, are included in a CD-ROM that can be obtained through WHO/Child and Adolescent Health and Development (CAH, e-mail: cah@who.int) or the Zinc Task Force.

3

How to translate these new global recommendations into country-level action

Box 1 Illustrative list of stakeholders

This list should be tailored to the specific context in each country

Ministry of Health

- Child Health Department/Programme
- Pharmacy and Essential Drugs Department
- Malaria Control Programme
- Directors of Reproductive Health, and HIV/AIDS Programmes
- Director of Primary Health Care
- Health Education Department
- Provincial and District Health Officers
- Training department

Ministry of Finance

- Director of Health Budgets

Professional Organizations

- Medical and Paediatrics Associations
- Nurses Association
- Pharmacists Association

Private Sector

- Manufacturers of zinc and ORS
- Importers and wholesalers
- Private hospitals and pharmacies
- Drug shops
- Traditional healers

Other

- National health policy makers
- Child health policy makers
- National poverty reduction strategy advocates
- Integrated Management of Childhood Illness (IMCI) programme managers
- Control of diarrhoeal disease programme managers
- Nutrition intervention programme managers
- NGOs
- Collaborating partners including multilateral (WHO, UNICEF, World Bank, etc.) and bilateral (USAID, U.K. Department for International Development, etc.) partners

The steps involved in the process to incorporate the new recommendations into the country's health policy include —

- Identifying key stakeholders
- Gathering clinical and scientific evidence
- Endorsing the new recommendations
- Revising/updating existing policy guidelines

Ideally, a comprehensive new policy document should present the background of the problem; explain the links to existing policies, programmes and strategies; clarify the roles of institutions and organizations that will be involved; and explain the details of the new recommendations.

Health policy environments and health systems vary from country to country, therefore there is no set process for introducing and changing health policies that will be guaranteed to work in every country. In this spirit, the following steps are not presented as an absolute roadmap to changing policy but rather as a guide to the elements that are likely to be involved in the development and adoption of a new diarrhoea treatment policy incorporating zinc and the new ORS solution.

3.1 Identifying key stakeholders

The stakeholders who will be involved in the decision-taking process should be identified. Those are likely to include government officials at national and local levels, civic society organizations such as nongovernmental organizations (NGOs), and professional associations, academic institutions and the private sector (Box 1). To ensure effective consensus for moving the policy change and implementation process forward, it is often helpful to establish a mechanism or structure, such as a national committee, representative working group or task force whose members should be chosen from among these stakeholders.

In particular, professional medical organizations such as the national paediatrics association are likely to be in a position to play an important role in defining the new policy and in influencing the key decision-makers.

An understanding of existing policies and programmes that will be affected by the new recommendations is also needed. These policies could include those directly related to health, such as the national health policy, but also those that are linked to social development (Box 2).

An analysis of the decision-taking process will be required to plan the next steps. Decision taking is complex and often involves many conflicting agendas. Barriers to decision taking should be identified so that unclear issues may be clarified and advocated to policy makers. The structure of the health care system has to be taken into consideration. For example, the health system is decentralized in some countries and many decisions are made at the local level. In this situation, it may be necessary to consult local decision-makers early in the process to get them on-board.

Box 2 Policies, programmes and strategies that may be affected by the new policy

- National health policies
- Child health policies and child survival strategies
- National poverty reduction strategies
- Integrated Management of Childhood Illness (IMCI)
- Control of diarrhoeal disease programmes
- Nutrition policies
- Millennium Development Goals
- WHO Strategic Directions for Improving the Health and Development of Children and Adolescents

3.2 Gathering clinical and scientific evidence

To make a policy decision, clinical and scientific evidence of the benefits of the treatment changes is needed. A summary of the scientific evidence justifying the new diarrhoea management recommendations is provided in Annex 1. Key references can also be found in Annex 2. Cost-effectiveness evidence can help persuade programme managers who are concerned about budgets.

Epidemiological data on childhood illness can be used to show the public health importance of diarrhoea in the country. Data on case management of childhood illness, including appropriate drug use, will be useful for showing the potential impact of the new recommendations.

The stakeholders that will be involved and affected by the new policy are diverse, including the public and private sectors. Each group will have its own perspective on the issues involved and will need their concerns to be addressed. Therefore the time and effort invested in assembling this documentation early on in the process of policy change will enable the champions of the new recommendations to have the information that may be needed to respond to concerns and questions, readily available.

Global bodies such as WHO, the United Nations Children's Fund (UNICEF) and the Partnership for Maternal, Newborn and Child Health can help facilitate the provision of evidence and information of experiences in other countries.

3.3 Endorsing the new recommendations

Discussions should be held with the key stakeholders early on in the policy change process. The goals of these discussions are to review —

- The nature and scope of the new recommendations
- How the new recommendations relate to the need of the country
- The implications for implementing the recommendations and resources required

The highest possible levels of the Ministry of Health should be involved in individual or small group meetings. These senior decision makers should learn enough about the new recommendations to chair subsequent meetings from a position of knowledge. It is also necessary to include in the

discussions professional organizations (medical, para-medical and pharmaceutical associations), donors and other partners, including NGOs who are interested in improving child health in the

country. The documentation described in the previous section (and in Annex 1) will be helpful for these discussions. The objectives of these discussions should be to obtain the endorsement of this new knowledge by professional associations and key stakeholders, and to develop and update existing official policies on the clinical management of diarrhoea.

Based on the evidence summary and any additional information obtained locally, national medical associations and/or policy makers should be in a position to clearly define national policy on the new recommendations for the management of diarrhoea, which should include a description of the levels or types of outlet from which ORS and zinc should be distributed.

A list of key questions regarding the policy change process which could help the task force or working group for planning purposes is illustrated in Box 3. These steps are not sequential and not all may be necessary if there is consensus on the policy change.

As an example, the statement on use of zinc in the management of diarrhoea made by the Indian Academy of Pediatrics (IAP) follows.

Box 3 Potential key questions for the policy change process

- Has there been an analysis and presentation of the epidemiological, social and behavioural evidence for change?
- Has an analysis of the political environment for decision-taking been made?
- Has an analysis and appraisal of the replacement options available been made?
- Have appropriate bodies/committees to oversee the process of the development and implementation of the new policy been set up?
- Has there been an analysis of health systems capacity for implementing the policy?
- Has there been consensus building and advocacy for change among appropriate stakeholders?
- Has a decision to change been officially made?

Recommendations of the IAP National Task Force for Use of Zinc in Diarrhoea, August 18–19, 2003.

- Based on studies in India and other developing countries there is sufficient evidence to recommend zinc in the treatment of acute diarrhoea as adjunct to oral rehydration. However, ORS remains the mainstay of therapy during acute diarrhoea and zinc has an additional modest benefit in the reduction of stool volume and duration of diarrhoea as an adjunct to ORS. Under all circumstances, oral rehydration therapy must remain the mainstay of treatment.
- Treatment of acute diarrhoea with zinc may have benefits on morbidity and mortality from other childhood infections.
- A uniform dose of 20 mg of elemental zinc should be given during the period of diarrhoea and for at least seven days after cessation of diarrhoea to children older than six months.
- Based on all the studies the group proposed that zinc salts, e.g. sulphate, gluconate or acetate may be recommended
- The industry should be encouraged to prepare zinc formulation which contains only zinc. Iron-containing formulations should not be used with zinc as iron interferes with zinc absorption.

3.4 Revising/updating policy guidelines

Based on the IAP statement and on the scientific evidence mentioned above, the Government of India created a committee to review the role of zinc as adjunct therapy with ORS solution for the

management of acute diarrhoea. Some of the committee's conclusions, which will constitute the new policy on the management of diarrhoea, follow —

- As the Indian Academy of Pediatrics, WHO and UNICEF have already endorsed the use of zinc as a supplement to ORS in the management of diarrhoea, the committee recommends the introduction of zinc in the national programme as an adjunct to ORS in the management of diarrhoea in children.
- A dosage of 20 mg of elemental zinc per day has been shown to be effective and safe, even for young infants, and therefore is recommended.
- The formulation of zinc to be used must have a shelf life of at least two years.
- Zinc sulphate, acetate and gluconate are all acceptable zinc salt formulations. However, zinc sulphate is low-cost, efficacious, safe and therefore optimal for the national programme.
- Administration of zinc is recommended through physicians in the Primary Care System. However, to have maximum impact on diarrhoeal diseases, zinc and ORS should be made available at community level.

4

Issues for the implementation of the new recommendations

This section focuses on key components in integrating the new ORS and zinc supplementation with the other recommendations for treatment of diarrhoea (Box 4). The section addresses components of implementation affecting both the public and private sectors.

Box 4 Key components for introducing the new ORS and zinc supplementation in the management of diarrhoea

1. Product issues

2. Supply management issues

- a) Technical
 - i. Drug regulatory considerations
 - ii. Review of the EML
 - iii. Review the STG and/or IMCI guidelines
 - iv. Training and supervision of health workers
 - v. Information, Education, and Health Survey (IEC) targeting the community
- b) Operational
 - i. Replacement of old ORS (if low osmolarity ORS is adopted)
 - ii. Plan phase-in zinc treatment with new formulation ORS
 - iii. Forecasting of demand and quantification
 - iv. Local production
 - v. Procurement
 - vi. Distribution
 - vii. Inventory management
 - viii. Private sector distribution
 - ix. Review of Quality Assurance Mechanisms
 - Pharmacovigilance
 - Product quality surveillance

3. Monitoring and evaluation

Although the steps are presented sequentially, this does not mean that steps must be conducted in this order. In reality, activities could be carried out in parallel to assure appropriate preparation and faster implementation. The different issues are discussed below.

4.1 Product issues

Many vitamin products and other nutritional supplements containing zinc are available commercially. However, it is uncommon for these products to have the recommended dosage of zinc. Therefore a product containing only zinc is required, although copper could be added. The product should be formulated in such a way as to mask the strong metallic aftertaste of zinc to enhance acceptability to children. Zinc salt formulations for administration to children could take the form of syrup or tablets. The specifications of zinc products for use in the management of diarrhoea are listed in Annex 3. A document entitled "Specification guidelines for zinc tablets and oral solution" to assist countries in the selection and procurement of quality zinc products is being developed in collaboration with the U.S. Pharmacopeia and should be available soon upon request to WHO/Children and Adolescent Health (CAH) or the Zinc Task Force.

4.1.1 Low osmolarity ORS

The formula of the new low osmolarity ORS is presented in chapter 2 with the reasons for changing the recommendations. All other characteristics of the ORS remain the same, including the instructions for reconstitution. The new ORS is packaged

in a sachet to be dissolved in 1 litre of clean water, although the packaging and labelling should be different enough to distinguish it from the previous product. If the country has established manufacturers for standard ORS, there may be a need to convince them to change the formulation. Guidelines to assist manufacturers in producing the new formula are available through WHO/

CAH. Reference to this manual can be found in Annex 2, and a copy of the manual is included in the CD mentioned before. Where local procurement of the new ORS is not possible, most international procurement agencies now have the new formula of ORS available, e.g. UNICEF has been procuring the new formula ORS through its suppliers since 2004.

4.1.2 Zinc syrup

Zinc syrups are relatively easy to develop and manufacture. The technology required to make such products is usually available in many countries. When considering whether syrups are appropriate for a programme, cost must be considered. This includes not just the price of the product but also the cost of storage and transportation. In addition, it is important to take into account the shelf life of syrups that may be shorter than the shelf life of other formulations such as tablets.

Syrups containing zinc may already be available in many countries. However, before being recommended for use in the management of diarrhoea, the following characteristics of the available formulations should be checked:

- The concentration of the zinc syrup should be 10 mg/5 ml or 20 mg/5 ml.
- Any soluble zinc salts, e.g., sulphate, gluconate or acetate, may be used for the formulation of the syrup.
- The syrup should contain only zinc. However, in some cases copper (1 mg/dose) could be added.
- Iron should never be added to a zinc formulation as iron may interfere with zinc absorption.
- The product should be manufactured following good manufacturing practices (GMP) for pharmaceuticals.
- The shelf life of zinc syrup should be at least two years when stored in appropriate conditions, away from light and in a dry cool place (<30°C).

4.1.3 Zinc tablets

For use in children aged 1-59 months, tablets should rapidly disintegrate when mixed in a teaspoon of clean water or expressed breast milk (dispersible tablet). Disintegration makes it easier to administer to children, especially to young infants. Besides their ease of use, these tablets are lighter than syrups, and much less expensive to store and transport. A dispersible tablet can be put in a small amount (about 5 ml) of clean water (or breast milk) in a spoon, and in less than a minute the resultant solution can be administered to the infant. Some form of taste-masking is essential to ensure acceptability by infants and young children.

As for syrups, it appears that any soluble zinc salts, e.g. sulphate, gluconate or acetate may be used in the formulation of the tablets. The shelf life of zinc tablets should be at least two years when stored in appropriate conditions, away from light and in a dry cool place (< 30°C).

Tablets can be formulated as 10 mg zinc tablets or 20 mg zinc tablets. However, it may be easier to have only one dosage available in a given country to avoid dosage errors. It may therefore be preferable to recommend production and procurement of 20 mg tablets and ensure that the tablets are scored to facilitate administering 10 mg to children less than six months of age. In this case, a whole tablet would be given each day to children six months and older, and half a tablet to children under six months of age. If 10 mg tablets were used, then two tablets would need to be given to the older age group each day.

Zinc tablets can be manufactured locally. However, the technology and quality processes to produce these tablets to GMP of pharmaceuticals are not always available in most countries. If local production is a requirement, local pharmaceutical companies interested in producing these tablets will have to develop the technology for dispersion and taste-masking. External assistance may be required.

4.2 Supply management issues

There are technical and operational considerations within the supply management. These incorporate the activities related to the regulation and appropriate use of zinc, through the development and dissemination of guidelines and the development and use of appropriate training and IEC strategies. The operational considerations incorporate the activities related to procurement and supply chain management, which ensure that zinc is available at the points of service delivery.

4.2.1 Technical considerations

4.2.1.1 Revision of medicine regulation

The regulatory changes required for the successful introduction of zinc include registration and regulations pertaining to the policies of prescribing, dispensing and sale of zinc.

Zinc and ORS must be authorized for sale on the market of the country. Zinc can be registered as a medicine or as a nutritional supplement. As zinc is being promoted in the treatment of diarrhoea, it is recommended that zinc be registered as a medicine to ensure that the national Drug Regulatory Authority (DRA) has the responsibility of assuring the quality of the product being marketed.

Market authorization in most countries involves a product registration process that includes the submission of a dossier of information on efficacy, safety and other properties. Most DRAs request a GMP certificate for pharmaceuticals, and a certificate that the product is being registered in the country of origin if the product is imported. With the new ORS formulation, the registration process will be greatly facilitated in countries where old formulation ORS is already registered.

The product registration process can take three months or more, depending on how often the registration committee in the country meets. If zinc is not already registered and a country wants to start implementation, most countries have mechanisms to fast-track the registration process for public sector programmes.

Even though zinc is being used to treat a disease, registration of zinc as a nutritional supplement may be possible and sometime faster, but it is not recommended as the production of the zinc tablets or zinc syrups may follow less stringent quality control measures and the promotion of zinc as treatment of diarrhoea may be more difficult. Even if zinc is already registered in a combination of other micronutrients and vitamins, re-registration as a mono-formulation for use in the management of diarrhoea will be necessary. If both zinc syrups and zinc tablets are potentially available for use in country, then each formulation should be registered separately.

The registration does not affect the delivery mechanisms or level of use of the product, as this is dependent on the scheduling or classification¹, which is a different regulatory process. This usually follows the policy decision and the recommendations of the treatment guidelines for diarrhoea. Registration as a medicine does not imply that the product use is restricted to health

¹ This is the legal status of a drug, e.g. prescription-only medicine, over-the-counter medicine, etc.

clinics or can only be obtained through medical prescriptions; zinc should follow the same delivery mechanisms as ORS.

The pharmaceutical scheduling or classification needs to be determined to ensure that the accessibility and availability of zinc in public and private health facilities — pharmacies, clinics, and dispensaries and over-the-counter shops, *dépôts pharmaceutiques*, *duka la dawa*, or chemical sellers—is in line with the new diarrhoea management policy. It is recommended that zinc be delivered as an over-the-counter product, like ORS, to facilitate its availability in all drug outlets, and improve its accessibility.

4.2.1.2 Revision of the Essential Medicines List

The new recommendations for the clinical management of diarrhoea refer to two new therapies that are now listed in the WHO model list of Essential Medicines (EML) —

- The new ORS (reduced osmolarity ORS) (included in WHO EML in 2003)
- Zinc salts (included in WHO EML in 2005)

It is important to update the national EML to include the above two products, as the EML guides the selection of drugs for national procurement and for the standard treatment guidelines (STGs). As most countries have not automatically adopted the new WHO EML that was revised in March 2005, submission of an application to the national EML committee for the inclusion of the new ORS and zinc will be necessary. It is not necessary to specify the particular salt of zinc in the EML, it is sufficient to mention 10 mg and 20 mg elemental zinc.

4.2.1.3 Revision of the Integrated Management of Childhood Illness guidelines or other standard treatment guidelines

All STGs must be revised immediately after the policy has been agreed on and published. The new STGs will constitute the basis for submitting the request to include zinc and the new ORS in the EML, and for the scheduling of the products according to the levels of distribution established by the programme.

After updating the STGs, IEC strategies should immediately be developed to ensure that the same messages are communicated to health care workers at every level of care in public and private facilities, and to members of the public.

In many countries, the STGs for children under the age of five are the Integrated Management of Childhood Illness (IMCI) guidelines. The national IMCI guidelines will therefore need to be revised to include both the new ORS formula and the treatment of zinc for diarrhoea. This revision has already been made to the standard generic IMCI guidelines by WHO/UNICEF. If there are other STGs, guides for health workers, curricula or handbooks, or other documents dealing with treatment of diarrhoea in children under the age of five, these will also need revising. For some of these materials, it may not be possible, due to the cost, to publish entirely new documents as soon as the new recommendations are adopted. In this case, countries may choose to publish an addendum to replace the diarrhoea section in the original guidelines, taking into account the three to six months needed to complete the documents, and print and publish them. These factors, as well as the availability of the product, should be taken into consideration when planning the dissemination of the guidelines and training and supervision of health workers.

Additionally, development of job aids according to type of health worker and level of care, revision of existing diarrhoea job aids, development or revision of tools for supervision, monitoring and evaluation should take into account the new diarrhoea treatment policy.

4.2.1.4 Training and supervision of health workers

A plan must be developed for disseminating the revised STGs. This must include providing the guidelines to the public and private sectors, and sensitisation and/or training of the health workers in both sectors. The training curriculum and materials for IMCI must be revised to reflect the guideline changes.

Training/sensitisation activities of health workers on the use of new ORS and adjunct zinc treatment for diarrhoea management must be done shortly before zinc is available at the health facility level. Carrying out the training too early may have negative effects, for example providers may begin recommending the new treatment before it is available and/or they may forget the key messages emphasized during the training when the medicines are finally available. Carrying out the training after the product has been available in the facilities may mean that health workers may have already developed habits of inappropriate use of zinc.

A plan for disseminating the new recommendations for diarrhoea management to health workers and training them in their application needs to be developed with the following questions in mind. Will there be a pool of trainers to train future trainers? At what level? Or will a central or regional pool of trainers conduct all the training? It will be important to maintain and assure the quality of training throughout the system such as ensuring that some trainers of the pool participate at each training level. In planning the training sessions, assure that funding of these activities is available at district level by incorporating funding into the district budget planning cycle or identifying external resources.

Job aids and training materials will need to be developed and field-tested. Additionally, information packages may need to be developed for specific groups of professionals (e.g. for paediatricians, for health centre staff, etc). Each package has to be aimed at the appropriate level. For higher level staff in particular, a training session is not likely to be sufficient to convince them to practice the new treatment recommendations for diarrhoea. Advocacy and sharing of the evidence through channels such as newsletters and professional organizations will be required early in the policy decision process to convince this important group of stakeholders.

In addition to the health facility workers, district and regional teams and paediatricians, any community health workers providing ORS treatment in the community will need to be informed and trained on the new ORS and on dose and administration of zinc. These community workers will have a role in the training of caregivers in home-based diarrhoea management.

After training the health workers or providing the new guidelines to them, some form of follow-up will be required, such as a retrospective review of prescribing practices or observation of consultations. Supervision will also have to incorporate the new guidelines.

4.2.1.5 IEC Strategies

Implementation of the new diarrhoea management recommendations, especially those that introduce treatment with which providers, and particularly patients, have little or no experience, requires considerable planning for behaviour change strategies and capacity building at all levels. Public awareness about the new recommendations must be raised using multiple approaches, including print, mass media, interpersonal communication, etc. It is crucial that these campaigns are coordinated with the sensitisation/training of health workers on the new recommendations to ensure that everyone is communicating the same messages. Some formative research may be necessary to guide the development of messages and strategies to target caregivers. Particular attention should be given to issues of adherence and how to encourage the caregivers to continue the zinc treatment for 10-14 days, when the ORS is usually only given for two days, by which

time the child may no longer have increased stool output,. An implementation plan consisting of types of strategies, target groups and timing of the interventions is essential.

A document entitled *Introducing Zinc in a Diarrheal Control Program: A Manual for Conducting Formative Research* by Dr Mark Nichter, Dr Cecilia S. Acuin and Ms Alberta Vargas, was produced to assist in the development and evaluation of messages to promote zinc supplements in the treatment of diarrhoeal diseases. This document is available at the following Web address, http://www.inclentrust.org/downloads/zinc_manual_02_21_05.doc, and is also included in the CD-ROM.

Some examples of IEC strategies or materials for the introduction of zinc treatment are —

- Brochure for community leaders
- Instructions for caregivers
- Radio and TV spots and other mass media channels (e.g. billboards)
- Audio tapes for health facilities, markets, other community events
- Incorporation of messages regarding new guidelines for management of diarrhoea into existing health communications programmes and packages (i.e. IMCI, breastfeeding, Vitamin A supplementation)
- Job aids (e.g. flip charts, counselling cards for health workers counselling caregivers in groups or one-on-one)
- Posters
- Use of “champions” among opinion leaders (sport, arts, or media personalities, politicians)

4.2.2 Operational Considerations

4.2.2.1 Replacement of old ORS

Countries may be reluctant to change treatments when there are large amounts of the old ORS formulation in the system. If the switch to new ORS has not yet been made, accurate estimates of the old ORS formulation in stock must be compiled as part of the replacement plan, and future procurements should be adjusted to ensure that there is no large stock of the old formulation in the system when the switch to the new formulation takes place.

Data on amounts of ORS that are on order can be obtained from the central medical stores, district stores and health facilities through a request by letter from a recognized authority. The procurement agency will often be aware of any ORS on order that has not yet arrived in the central stores.

As old ORS is not dangerous to use, it is not necessary to withdraw stocks. It is simply a question of planning the introduction of the new ORS in such a way that both products are not in circulation concurrently. This is not because the mode of administration of the new ORS is any different, but simply to avoid confusion created by slightly different presentations among health workers and more importantly caregivers. Existence of old ORS should not be a barrier to initiating zinc supplementation.

4.2.2.2 Plan phase-in of zinc treatment

The new policy can be implemented either through a phased implementation or through an immediate nationwide rollout. The planning of this component depends on the option chosen. Phased implementation could be geographically, with some areas or districts selected for early implementation, or it could be according to health system level, with some levels of the health system selected for early implementation.

The advantages of a phased implementation include —

- Lower start-up costs for the implementation
- The ability to test the implementation strategies and identify and correct any problems with the materials or methods
- The uptake of the new recommendations in the health facilities can be monitored and modelled, thus allowing for better forecasting of the demand for ORS and zinc

On the other hand, a nation wide implementation plan requires greater start-up costs, good pre-testing of IEC and training materials, and better coordination of all activities to ensure that the implementation is successful.

4.2.2.3 Forecasting of demand and quantification

Forecasts of demand and quantification are different. A forecast of demand is based on theoretical need often based on projections of utilization, whereas quantification is a more accurate estimate of what is required based on actual utilization rates and service use or consumption patterns and also budget.

Box 5 Key questions to consider when forecasting the potential demand for zinc

- What method is currently used for forecasting of ORS?
- How are forecasts validated and how are the data managed?
- Are adequate buffer stocks planned at relevant levels?
- Are parallel efforts for national procurements and grants appropriately harmonized?
- What method of quantification will be used to determine the estimates and what are the data limitations?
- Will the implementation be piloted in a few districts then scaled up gradually throughout the country or will there be a nationwide rollout?
- What is the expected uptake of the new policy over time within each health facility and/or district?

Key questions when making the forecasts are listed in Box 5.

The initial step is to determine if the demand forecast is for the public sector network alone, for community-based distribution, or for the private sector as well. Several different methods can be used to compile a forecast of demand, including consumption-based methods and morbidity-based methods.

For ORS, the method based on past consumption could be used as a starting point. With time this estimate can be improved, as it is expected that the new ORS may be better accepted by children and caretakers and so demand may increase.

In the case of zinc, however, there is no data on previous consumption, so the appropriate method of forecasting to use is based on morbidity, at least during the initial years of implementation. Getting adequate morbidity data can be challenging due to the potential inaccuracies of the data in the health management information systems (HMISs), and often best possible estimates must be made from data that do exist.

There must be a clear understanding of the source of the morbidity data and the treatment-seeking behaviours with respect to diarrhoea in the country. HMISs usually collect data from the public health facilities only, possibly resulting in an under-representation of the morbidity burden of diarrhoea in the country.

A very rough way of forecasting demand for zinc in the absence of good HMIS data is to link the potential need to the procurement of ORS or its distribution to the public. For example, if it is assumed that a patient with diarrhoea will use an average of two sachets of ORS, 10-14 tablets of 20 mg zinc will be necessary. Of course this is limited by the accuracy of the ORS distribution and probably only includes the public sector distribution. However, in some countries the majority of cases may use home fluids instead of ORS and so the forecast of zinc demand in these cases, if based on ORS consumption, may be an underestimate of true requirements.

A team approach to forecasting demand for zinc should be recommended so that stakeholders from the child health division and HMIS are involved in addition to the central medical stores personnel. If the private sector will be involved in providing zinc supplementation, the stakeholder group should be enlarged to include its representatives, such as the national chemical sellers association or equivalent. This allows all involved to discuss potential errors in forecasting data and arrive at a consensus on the best method of forecasting.

A phased implementation has the advantage of allowing for the collection of data that would enable better estimates of the uptake of the new recommendations at the health facilities, thus improving the estimates of the potential demand before the nationwide implementation.

As zinc treatment is so new and there are complexities associated with forecasting demand, there may be a need to develop preliminary estimates of future demand of zinc for suppliers who need to plan their production. These estimates will have to be reviewed continually and adjusted as new information becomes available.

The forecasts can then be used to cost out the requirements and carry out quantification for procurement based on available budget and buffer stock requirements. It is therefore important to identify early on how zinc procurement will be financed — through the Ministry of Health, through donors, and by the out-of-pocket contribution that will be expected from consumers — to ascertain what budget implications there may be on the quantification process.

4.2.2.4 Local production

The discussion of local production applies to ORS and zinc.

If ORS is produced locally, ensure the switch to the new formulation is made as long as the production is according to GMP. Poorly manufactured ORS can cause serious problems. For example, if the particles are not equally sized, settling in the package may lead to a higher concentration of one of the ingredients. If all the content of the packet is not added to the water for reconstitution, a higher concentration of potassium, for example, could potentially be fatal. It is therefore important that local ORS production meets GMP standards to ensure the best quality product and that GMP standards are adequately understood and adhered to by manufacturers. Recently revised guidelines for the production of the new ORS are available at WHO/CAH and can also be found on the CD-ROM.

The local production capacity for zinc syrups or tablets should be assessed. These should be produced according to the U.S. Pharmacopeia monographs and to GMP standards. If a local manufacturer cannot develop an appropriate formulation of tablets (with the ideal properties of adequate taste masking and dispersibility), external assistance may be required.

If local production capacity for zinc does not exist, or the terms for importing raw material are unfavourable (some countries have a very high tax to pay on imported raw materials), international procurement of zinc syrup or tablets will be necessary. It is still possible, though, to explore local capacity for re-packaging of imported zinc tablets in order to incorporate messages in local language to the package or to ensure that the pack size is a full course of treatment. Another option is to consider a “diarrhoea management kit” where ORS sachets and zinc tablets are co-packaged in an attractive package, with easy to follow instructions. The latter recommendation needs to be considered carefully given that in some countries home fluids are more generally used than ORS and that non-dehydrated children rarely receive ORS. However, any case of diarrhoea, dehydrated or not, should receive zinc. The cornerstone of diarrhoea case management is ORT, and the message should not be confused, forcing caretakers to purchase a kit, when all they would need is zinc.

4.2.2.5 Procurement

“An effective procurement process ensures the availability of the right drugs, in the right quantities, at reasonable prices, and at recognized standards of quality¹”. The key questions that need to be asked in developing a procurement plan for the new ORS and zinc are listed in Box 6.

Often actual procurement and financing of the procurement occur in different departments or ministries or through donors. There is a need to coordinate activities to ensure synchronization between the financing activities and the requirements of the procurement cycle.

Box 6 Key questions on procurement of the new ORS and zinc

- What procedures and/or systems exist for managing the procurement process?
- What type of procurement exists: centralized (pooled) or decentralized?
- Is the system transparent and efficient?
- What funds are to be used for the purchase of the new ORS and zinc?
- Is there a local source of the new ORS and/or zinc or will it be imported?
- What is the anticipated duration of the procurement cycle from product selection to the arrival of the product?
- Are there systems in place for monitoring supplier performance and enforcing the procurement contracts?
- Is there a quality assurance system established in the procurement process (pre-qualification of suppliers, enforcement of GMPs, etc.)?
- Is there a need to repackage the product, and if so, who will do this?
- Is there a need to prepackage the product, and if so, who will do this?

For the implementation of the new policy, which combines the new ORS and zinc for diarrhoea treatment, a procurement plan that considers the distribution strategy (including the public and private sectors) must be developed. Both zinc and ORS should be included in this plan. Although zinc is initially a new product, the plan for the new ORS should take into consideration lead time², delivery times, as well as stock levels and consumption of ORS.

This procurement plan must also include information on the procurement method to be used, i.e. whether to use open tender, restricted tender, competitive negotiation, or direct procurement. A detailed discussion on the advantages and disadvantages of these methods can be found in other resource texts¹. To obtain the best prices, however, competitive procurement is generally recommended, although the limited number of suppliers of zinc at this time may mean that the cost benefits of competitive procurement may not always be achieved. Depending on the source of funds, if zinc has been registered as a medicine in the country, it will be necessary to purchase a formulation of zinc that is produced by a pre-qualified supplier of UNICEF, or that, at least, has been manufactured to pharmaceutical GMP standards. At the time of writing, UNICEF is in the process of identifying qualified suppliers of zinc. UNICEF supply division are exploring with

several international manufacturers and awaiting their attainment of UNICEF pre-qualification standards. It is expected that by mid-2006, UNICEF will have identified and pre-qualified suppliers and that countries will be able to procure zinc through UNICEF.

Decisions on packaging of zinc will have to be taken if the product identified for procurement is not packaged appropriately (in a complete dose package) or if a combined packaging of ORS with zinc tablets is required. In this case a firm needs to be identified to do this re-packaging. If zinc is to be procured for public and private sector distribution, it needs to be determined whether the same packaging should be used in public and private sector. Language requirements for packaging should be established to help ensure that both prescribers and consumers have the information needed to use the product correctly.

¹ Management Sciences for Health and World Health Organization. 1997. *Managing Drug Supply: The Selection, Procurement, Distribution, and Use of Pharmaceuticals*. 2d ed. Hartford, CT: Kumarian Press.

² Time between order of the product and time when the product is available for use in health facilities.

Irrespective of the procurement method selected, systems need to be put in place to ensure that the products procured are of appropriate quality. This may be achieved either through pre-qualification or post-qualification of suppliers as part of the competitive bidding process. Additionally, there must be a system in place for monitoring supplier quality assurance and quality control performance and for resolving any identified problems.

Once tender documents have been developed, the usual procurement process will be initiated and managed, and supplier performance will be monitored. There may be a need for technical assistance in the procurement in which case a qualified resource for technical assistance should be identified and contracted with.

4.2.2.6 Distribution

Once the new guidelines on diarrhoea management have been endorsed and included in a National Policy, with a clear mandate for implementation, and a sustainable supply of zinc and ORS established, it will be important to review and strengthen distributions channels. It should always be kept in mind that zinc supplementation is an adjunct treatment to ORT. Therefore, in the treatment of diarrhoeal diseases it should always be promoted together with ORS solution or other home available fluids recommended locally for the management of diarrhoea.

To achieve the desired coverage, both public and private distribution of zinc and ORS will be required. This section covers only the public sector distribution including health facilities, child care facilities (where trained workers identify cases and counsel parents/caregivers), outreach services (routine semi-annual ‘child health weeks’, ‘catch-up rounds’, polio ‘mop-ups’, other interventions using social mobilization) and community health workers. Zinc treatment should be integrated into the existing distribution such that it is distributed in the same way as the new ORS, rather than create a parallel distribution for zinc supplements. There may be deficiencies in that system that should be strengthened to assure constant availability of zinc and the new ORS.

The distribution of zinc and the new ORS will differ from country to country, depending on how the public distribution system is organized, and whether or not a central medical store plays a role in the distribution system so it is essential to understand what type of distribution system prevails in the public sector of the country. In a “pull” system, the health facilities order medicines and supplies from the central medical stores or from suppliers based on their own determination of their needs. In a “push” system, the central medical store determines the types and quantities of medicines and supplies to be sent to each health facility based on the information they have received about the needs of the health facilities.

It is important to review the distribution system and study the availability of drugs at peripheral levels to identify strengths and weaknesses, such that the weaknesses in the distribution system do not lead to failure of the policy implementation. Transport and storage capacity at central and peripheral levels are also important aspects to consider.

Another important aspect to consider under distribution is whether the zinc and the new ORS treatment will be dispensed free of charge, or whether there will be a fee associated with it, for example, in countries where there is cost recovery and user fees in the public health system. The fee could be cost price plus a mark-up or a subsidized price.

4.2.2.7 Inventory Management

Inventory management measures need to be assessed and upgraded, or established if they do not already exist, at all health facilities. This is to ensure that the stock of zinc and the new ORS are

managed appropriately to prevent stock-outs and to ensure that wastage due to expiry is minimal. Key questions are listed in Box 7.

Box 7 Key questions for inventory management

- What inventory control mechanism is in place and is it reliable? Is a physical check of drugs carried out at least annually?
- What is the average stock turnover time and is there a policy and practice of issuing stock according to first expiry/first out at all levels?
- Are there functional management information systems to manage product flow?
- How well is the shelf life of products managed throughout the existing supply chain? What systems are in place for dealing with expired products?
- Are adequate security measures in place to prevent theft of stored products?

Mechanisms will be needed to ensure that store management tools such as stock cards are available; that records are kept and updated regularly; and that physical checks are regularly performed. If computer software is in place, it may have to be adapted to incorporate the data needed for managing the new products. It is important to ensure that products do not expire before they are used and any expired stock is efficiently removed from the facilities and stores.

4.2.2.8 Private sector distribution

The options for distribution of zinc and the new ORS in the private sector will vary country by country and possibly even region by region within the country. A rapid assessment will identify the strengths and weaknesses of various options and types of private sector outlets (e.g. clinics, pharmacies, drug shops) that can potentially distribute the new ORS and zinc.

This assessment will lead to selection of the most appropriate conduit through which to channel the new ORS and zinc distribution. A plan of work with private providers will have to be developed. The private nonprofit providers (e.g. NGOs and faith-based clinics) should also be included in the assessment as they contribute greatly to health services coverage in many countries.

It is essential that private sector providers be oriented to the new treatment guidelines for diarrhoea management in children under the age of five. Professional associations and other organisations should also be made aware of the reasons and evidence for the recommendations and the actual treatment guidelines.

In countries where the private sector is an important source of drugs for the treatment of children under the age of five, the availability of both the new ORS and zinc supplements (in both tablet and syrup form) and their appropriate use should be encouraged. In countries where there are ongoing interventions in the private sector (e.g. franchising or accreditation) it will be important to ensure that new ORS and zinc treatment is added to the curriculum and training materials, and to the list of medicines authorized for sale and monitoring tools. In some countries and situations, social marketing of zinc is a possibility to consider.

Countries that have unpaid community volunteers outside the public health system providing curative services should investigate how to include these individuals in the process. This will help clarify what training and capacity gaps exist in the new treatment options and what incentive and sustainability mechanisms are effective in each population/culture.

4.2.2.9 Quality assurance

The main quality assurance issues regarding implementation of the new recommendations are related to product efficacy, product safety (pharmacovigilance), product quality and post-marketing quality surveillance. Countries may already have surveillance systems that monitor ORS production;

however, such systems may not exist for other medicines, and are definitely not in place for nutritional supplements. Quality assurance in production process is key, and the best mechanism to ensure a product of quality. Building capacity in existing structures that collect similar information for other essential medicines could be considered to make the best use of available human resources.

Pharmacovigilance

- Side effects of the new ORS

Because the new ORS contains less sodium chloride, concerns were raised that introducing it would lead to an increased incidence of hyponatraemia. Indeed, studies evaluating the efficacy of the new ORS had shown that although more efficacious than the old formulation, use of the new ORS was associated with an increased risk of transient, asymptomatic hyponatraemia. Pharmacovigilance studies have therefore been undertaken in Bangladesh and in India to evaluate if this increased risk of transient asymptomatic hyponatraemia observed in the hospital-based studies was translated into an increased risk of symptomatic hyponatraemia when the new ORS was used on a large scale. Results from these two studies, which included about 100,000 adults and children hospitalised with diarrhoea, indicate very clearly that use of the new ORS is not associated with an increased risk of symptomatic hyponatraemia. In fact, in Bangladesh the incidence of symptomatic hyponatraemia was divided by two after the introduction of the new ORS when compared to periods when only the old formula was available.

- Side effects of zinc supplementation

To date there has been no report of severe adverse reaction from any form of zinc supplementation for the treatment of diarrhoea. Trials have included more than 9,100 children who have participated in efficacy trials in both the placebo and zinc study arms and nearly 12,000 child-years of observation from one large effectiveness trial. The zinc doses have ranged from 5-45 mg per day and have been well-tolerated in diverse settings. Trials have found no differences in adverse reactions based on the different zinc salts (sulphate, acetate and gluconate) used in supplementation trials.

Presently, the only reported side effect of zinc supplementation has been vomiting. Of the seven trials that have reported on incidences of vomiting, only two reported more vomiting in the children who received the zinc than in the placebo group. One trial reported higher vomiting in the zinc versus the control group when zinc was given with multiple micronutrients but not when given alone.

Copper status has been evaluated in four trials. Three of the four trials did not find a difference in serum copper status after supplementation. One trial did find a significant trend of decreased copper level when comparing zinc supplemented children to non-zinc supplemented children. However, these children were malnourished with persistent diarrhoea at baseline. Overall, there is no substantial evidence of short-term zinc supplementation for the treatment of diarrhoea adversely affecting copper status.

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

- Reporting of adverse drug reactions

Despite the absence of serious adverse effects linked to the use of the new ORS or to the use of zinc in the literature, once treatment becomes more widespread, mechanisms should be in place for active reporting of adverse events associated with their use. This may be ensured by the establishment of a regular reporting system through the health facilities and/or through special studies. This system for monitoring adverse events must be developed within the systems for monitoring adverse events for other medicines. Forms for recording adverse events should be provided to the health facilities. At each level of the health system, a point person must be appointed to collate the data and a system for reporting back to the central level should be developed.

Product quality surveillance system

Product quality surveillance must be integrated at all levels of the health system to ensure that the new ORS and zinc syrups and/or tablets available in the market are of the appropriate quality. A comprehensive system includes ensuring quality during drug registration, procurement, and distribution through the public and private sectors. It also includes a mechanism for removing from the supply chain any products found to be of inappropriate quality.

Regular monitoring of batch quality control by the manufacturer may also be a necessary requirement.

4.3 Monitoring and evaluation

Monitoring and evaluation (M&E) is essential and occurs throughout planning and implementation. Planning for M&E needs to be done early and integrated throughout the implementation process so that monitoring data can be used to guide any changes in implementation strategies by governments, and external stakeholders. It is essential to develop an M&E plan that includes adequate indicators to track implementation progress and performance relative to defined/established targets. A situational analysis study prior to introducing the new ORS and zinc for the treatment of diarrhoea would be useful to guide the implementation and to serve as a baseline measure. This baseline should include basic data on availability of ORS and zinc, and management of diarrhoea in the public and private sectors.

As a component of interventions to monitor and enhance the quality of health services, specific monitoring and supervision procedures and schedules should be developed to maintain the integrity of diarrhoea management activities through both public and private channels. It will be important to monitor the use of zinc and whether there is any influence on the rate of use of antibiotics in the treatment of diarrhoea and to ensure that zinc does not get used preferentially to ORS.

Training in supportive supervision may be needed, and feedback mechanisms will need to be established if not already in existence. All M&E tools developed to monitor implementation of zinc treatment need to be reviewed and updated, if necessary, to respond to any changes in the implementation strategy.

Data for monitoring and evaluation can be obtained from existing surveys, such as Demographic and Health Survey (DHS) and health management information system (HMIS) data, or through special studies. The decision on which information source(s) to use depends on each country context and the type of information systems available. Types of information systems include —

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- DHS — These nationally representative household surveys provide data for a wide range of monitoring and impact evaluation indicators. This is a useful source of information on caregiver practices
 - Multiple indicator cluster surveys (MICS) — Household surveys
 - HMIS — Most countries have an existing HMIS system that provides basic information on mortality and morbidity rates
 - Drug management information systems may exist to provide information on management of drug supplies
 - Adverse drug reaction/pharmacovigilance reporting systems
 - Special studies — In the absence of good data to monitor the policy, it may be necessary to carry out special research to obtain particular data (e.g. health facility surveys using exit interviews, retrospective record reviews and stock records)

Some examples of M&E indicators are listed below —

- Process indicators
 - % of health care staff trained in the management of diarrhoea including new ORS and a 10-14 day treatment with zinc
 - Zinc and new ORS available at the central storage facility
 - % of health facilities and storage facilities and private sector outlets with ORS and zinc available
 - % of facilities with the revised treatment guidelines, e.g. the revised IMCI guide available
 - % of cases of diarrhoea in children under the age of five prescribed or sold zinc and the new ORS
- Outcome indicators
 - % of cases of diarrhoea in children under the age of five treated with a course of zinc supplementation for 10-14 days, in addition to ORS
- Knowledge, attitudes and practices indicators
 - % caregivers who are aware that zinc is an appropriate treatment for diarrhoeal disease
 - % medical providers who believe that zinc is an effective treatment for diarrhoea in children under the age of five

Summary of the evidence

1. Zinc supplementation and the treatment of acute diarrhoea

Duration of the episode

With regard to the time from enrolment in the study to recovery from diarrhoea, this review showed clearly that zinc supplementation has a significant beneficial effect on the clinical course of acute diarrhoea. In 11 of 12 studies, zinc supplementation was associated with a reduction in the duration of the episode, and in eight, the reduction was statistically significant. From the pooled analysis of these studies it can be estimated that zinc supplementation reduces duration of diarrhoea episode by up to 25%.

Proportion of episodes lasting more than seven days

Five studies recorded data on the proportion of episodes lasting more than seven days. Results of all these studies showed a trend towards a reduced proportion of episodes lasting more than seven days in children receiving zinc supplementation, and in one study, the reduction was statistically significant. Again, the pooled analysis of these studies showed that zinc supplementation can decrease by about 25% the proportion of episodes lasting more than seven days, therefore significantly reducing the proportion of diarrhoea episodes becoming persistent.

Stool volume

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

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

2. Zinc supplementation and the treatment of persistent diarrhoea

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

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

Zinc-supplemented children with persistent diarrhoea had a 24% lower probability of continuing diarrhoea (95% Confidence Interval [CI]: 9%, 37%) and a 42% lower rate of treatment failure or death (95% CI: 10%, 63%) than those in the control group. It should be noted that there tended

to be a greater effect in subjects less than 12 months of age who were male, or who had wasting or lower baseline plasma zinc concentrations.

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

3. Zinc supplementation and the prevention of acute and persistent diarrhoea

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

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

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

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

4. Zinc supplementation and the treatment and prevention of bloody diarrhoea

A number of studies have shown that zinc supplementation, either continuous or short course, had a positive impact of the prevalence of dysentery in the month following the supplementation.

In addition, studies conducted during acute shigellosis have shown that zinc supplementation significantly improves seroconversion to shigellacidal antibody response and increases the proportions of circulating B lymphocytes and plasma cells and the IgA-specific immunoglobulin response. For all these reasons, it is clear that zinc supplementation should be given as an adjunct to antibiotic treatment of bloody diarrhoea.

5. Zinc supplementation and cost effectiveness evaluation

A recently published study analysed the incremental costs, effects and cost-effectiveness of zinc used as adjunct therapy to standard treatment of acute childhood diarrhoea, including dysentery, and reassessed the cost-effectiveness of standard case management with ORS.

A decision tree was used to model expected clinical outcomes and expected costs under four alternative treatment strategies. The best available epidemiological, clinical and economic evidence was used in the calculations, and the United Republic of Tanzania was the reference setting. Probabilistic cost-effectiveness analysis was performed using a Monte-Carlo simulation technique and the potential impacts of uncertainty in single parameters were explored in one-way sensitivity analyses.

In this study, ORS was found to be less cost effective than previously thought. The use of zinc as adjunct therapy, however, significantly improved the cost-effectiveness of standard management of diarrhoea for dysenteric as well as non-dysenteric illness. The results are particularly sensitive to mortality rates in non-dysenteric diarrhoea, but the alternative interventions can be defined as highly cost-effective even in pessimistic scenarios.

From this study there is sufficient evidence to recommend the inclusion of zinc into standard case management of both dysenteric and non-dysenteric acute diarrhoea.

6. Zinc supplementation and irrational use of antibiotics

Excessive use of antibiotics for diarrhoea is a major contributing factor towards increasing rates of antimicrobial resistance in developing countries. A study of antibiotic use in a rural area of Bangladesh found that 26% of purchased drugs were antibiotics, which were most frequently purchased for children aged 0–4 years to use for diarrhoea; 48% of antibiotics were purchased in quantities of less than a single day's dose. These practices have probably not led to improvements in health and may have promoted the emergence and persistence of drug-resistant microorganisms.

Zinc therapy for diarrhoea has been shown to be beneficial in controlled efficacy trials, and it is of interest to determine if availability of zinc syrup for treatment of diarrhoea would satisfy the demand for a medicine for diarrhoea, thus reducing the use of antibiotics, without competing with the use of oral rehydration therapy (ORT).

A community-based controlled trial was conducted in Matlab (Bangladesh): wherein 30 service areas (clusters) around Matlab Treatment Centre, each with about 200 children aged 3–59 months, were randomly allocated to intervention or comparison areas. One community health worker served each cluster. All children aged 3–59 months were included in the study.

Antibiotic use for the treatment of diarrhoea was about 70% less in the zinc intervention areas. In addition, visits to pharmacists and village doctors were significantly less; visits to village doctors and pharmacists are among the most important determinants of inappropriate antibiotic use. The significant reduction in antibiotic use and related behaviours in the intervention group demonstrate that the benefits of zinc supplementation extend well beyond reducing childhood morbidity and mortality. Zinc supplementation for diarrhoea with education programmes, in addition to ORT, could reduce inappropriate antibiotic use that is leading to antimicrobial resistant pathogens.

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Specifications of zinc products for use in the management of diarrhoea

1. Dosage

- Each individual dose of zinc should contain 10 mg or 20 mg of elemental zinc.
- For syrups, the concentration of elemental zinc should be either 10 mg/5 ml or 20 mg/5 ml.
- For tablets, each tablet should contain either 10 mg or 20 mg of elemental zinc. Tablets containing 20 mg of elemental zinc should be scored.

2. Type of zinc salt

The zinc salt used to prepare syrups or tablets for use in the management of diarrhoea should be soluble in water. Therefore, only the following zinc salts should be used —

- Zinc sulphate
- Zinc acetate
- Zinc gluconate

3. Type of tablets

As the zinc tablets will be used in infants and young children, it is essential that the tablets be dispersible. This means that the tablets should be completely disaggregated in about 30 seconds or less than 60 seconds in 5 ml of tap water or breast milk.

4. Taste-masking

The three zinc salts have a bad metallic taste that led to the use of zinc as a vomiting agent until the beginning of the twentieth century. To get infants and young children to take zinc tablets or zinc syrup repeatedly every day for 10-14 days, it is essential that this metallic taste be totally masked.

5. Costing

It is important to keep the cost of the zinc dose as low as possible. Arbitrarily, we would suggest that the cost of one dose of zinc do not exceed US\$ 0.02.

6. Packaging

Tablets and syrups should be packaged to provide a full treatment of 10-14 daily doses of zinc (i.e. for syrups containing 20 mg/5 ml, bottles should contain 50-75 ml of syrup; for tablets, a blister should contain 10-14 tablets).

7. Shelf life

The zinc product should have a shelf life of at least two years.

