Proposal to include an additional listing of co-packaged ORS and zinc for management of diarrhea in children on the WHO Model List of Essential Medicines for Children

Application for submission to the 22nd Expert Committee on the Selection and Use of Essential Medicines

The Diarrhea Innovations Group

PATH

This application was prepared by members of the Diarrhea Innovations Group (DIG), a global network of innovators committed to reducing child deaths from diarrhea through the development of new diagnostic and therapeutic technologies and approaches. DIG is housed at PATH.

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Abbreviations

aOR	adjusted odds ratio
CFR	case fatality ratio
CHAI	Clinton Health Access Initiative
CI	confidence interval
DALY	disability-adjusted life year
DIG	Diarrhea Innovations Group
DTK	diarrhea treatment kit
EML	WHO Model List of Essential Medicines
EMLc	WHO Model List of Essential Medicines for Children
GAPPD	Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea
GBD	Global Burden of Disease Study
HIV	human immunodeficiency virus
ICD	International Classification of Diseases
LMIC	low- and middle-income countries (as defined by the World Bank)
MCA	Department of Maternal, Newborn, Child and Adolescent Health (World Health Organization)
NA	not applicable
NEML	national essential medicines list
NF	National Formulary (United States Pharmacopeia)
OR	odds ratio
ORS	oral rehydration salts
SDI	Socio-demographic Index
UNICEF	United Nations Children's Fund
USP	United States Pharmacopeia
WHO	World Health Organization
zinc	zinc sulfate

1. Summary statement of the proposal for inclusion of co-packaged oral rehydration salts and zinc sulfate on the World Health Organization Model List of Essential Medicines for Children

This application is for the addition of co-packaged oral rehydration salts (ORS) and zinc sulfate (zinc), as an additional single item, to the core World Health Organization (WHO) Model List of Essential Medicines for Children (EMLc).

Currently, ORS is listed in section 17.5.1 (Oral rehydration) of the current EML and EMLc. Zinc sulfate tablets are also included in section 17.5.2 (Medicines for diarrhoea) of the current EML and EMLc, with the following note: "In acute diarrhoea, zinc sulfate should be used as an adjunct to oral rehydration salts."[1,2]

The evidence presented in this application suggests that addition of a new listing for both products co-packaged as a single item would support the long-standing 2004 WHO/United Nations Children's Fund (UNICEF) recommendation that acute diarrhea in children be treated with both ORS and zinc.[3] Furthermore, a single listing for co-packaged ORS and zinc would provide a number of public health and normative benefits that would ultimately help bring down global mortality and morbidity rates associated with the burden of diarrhea.

As we approach the fifteenth anniversary of this recommendation, a median 42% of children with acute diarrhea receive ORS and less than 7% receive both ORS and zinc.[a,4] Diarrhea remains the second leading infectious cause of death in children younger than 5 years of age. It is also a significant contributor to growth stunting and deficits in cognitive development, with far-reaching implications for the health of families, communities, and emerging economies.

Lifesaving properties, safety, and cost-effectiveness of ORS and zinc for the treatment of diarrhea have been well-demonstrated,[5] with several improvements highlighted below and further in section 8:

- Low-osmolarity ORS reduces stool output, vomiting, and need for unscheduled intravenous therapy.
- Zinc has been shown to reduce the duration and severity of diarrheal episodes and prevent future episodes.
- In a review of 157 studies, use of ORS was found to have reduced diarrhea-specific mortality by 69% (95% confidence interval [CI]: 51-80), and had a treatment failure rate of only 0.2% (0.1-0.2).[6]

a. These figures are based on available data from 49 and 26 countries for ORS and zinc, respectively. The figures would likely be lower if countries not reporting ORS and zinc coverage were included in the analysis.

- A review of 13 randomized trials[7] from low- and middle-income countries (LMIC) found that zinc administration for diarrhea management significantly reduced all-cause mortality by 46% (relative risk 0.54; 95% CI: 0.32-0.88), and hospital admission by 23% (relative risk 0.77; CI: 0.69-0.85).[b]
- Zinc has been shown to decrease the duration of diarrhea by 25%, as well as provide subsequent protection from recurrence in the 2 to 3 months following treatment.[8,9,10]

Despite these important benefits, access to ORS and zinc remains a challenge in low-resource settings, and the rate of co-administration of both products is extremely low. Of 11 of the 15 highest-burden countries with available data, 6 (~55%) had ORS and zinc coverage levels of 2% or less.[11] Despite the instruction on joint administration, the two products are treated very differently on national essential medicines lists (NEMLs; see section 8b), creating a number of barriers impeding access, including national-level policy and procurement challenges.

A number of significant public health benefits from introduction of co-packaged ORS and zinc have already been demonstrated (see section 9b), including:

- Increased uptake and coverage of ORS and zinc (as a combination therapy and as individual components dispensed together), reducing the risk of severe health consequences of chronic diarrhea and stunting, acute diarrhea, and zinc deficiency among children.
- Improved adherence to the combined therapy of ORS and zinc.
- Improved adherence to/preparation of individual components (e.g., correct concentration of prepared ORS, completion of a full course of zinc).
- Improved dispensing practices by health care workers.
- Reduced hospitalizations due to diarrhea.
- Reductions in inappropriate antibiotic prescribing and use.
- Enhanced satisfaction levels by caregivers of ORS and zinc relative to status quo products.
- Enhanced opportunities for developing private-sector models and leveraging value chains to improve availability and access closer to the household level.

In addition, this inclusion could lead to a number of normative and other benefits, such as:

- **A cascade effect.** Global treatment guidelines and the essential medicines listings serve as important guides for countries in their development of NEMLs and procurement and supply of medicines for donation and local medicine production, as well as training of health care providers.[12,13] Listing of co-packaged ORS and zinc has the potential to foster an enabling environment for country-level policy work to prioritize access to treatment and incorporate co-packaged ORS and zinc into national health programs.

b. Estimates modeled with the Lives Saved Tool also show that if 15 key interventions (inclusive of ORS and zinc) were scaled up by 80% in the 75 Countdown to 2030 countries, 95% of diarrheal deaths in children younger than 5 years could be prevented by 2025.

- **An awareness effect.** WHO EML listing stands to increase recognition and reinforcement among policymakers and health care professionals of co-administered ORS and zinc as a cornerstone of childhood diarrheal treatment worldwide.
- **Availability effect.** Listing of a co-packaged product can guide the selection, procurement, and supply of medicines in the public sector, schemes that reimburse medicine costs, and medicine donations, from the national level down to provincial/regional and district levels within countries.[14]
- **A manufacturer effect.** The listing may catalyze increased demand and spur local medicine production, with manufacturers responding and creating more market competition.[12]

Clear global guidance is a critical first step in creating an enabling environment to facilitate the uptake of co-packaged ORS and zinc at the national level across low-resource countries, and to ultimately increase access to and use of the recommended treatment to save and improve lives, thereby contributing to universal health coverage. As part of this application effort, the Diarrhea Innovations Group is also committed to laying down the necessary framework for the next phase of this work, which will focus on translating global policy into national adoption and scale-up. The concept note in Annex I outlines the initial thinking about the next steps, following the listing of co-packaged ORS and zinc on the WHO EMLc.

2. World Health Organization technical department and focal points supporting the application

The relevant WHO technical department is the Department of Maternal, Newborn, Child and Adolescent Health (MCA). This department is within the cluster of Family, Women's and Children's Health, which falls under the Deputy Director-General for Programmes.

Our contacts in the preparation of this application have been:

- Professor Per Ashorn, MD, PhD, Scientist, MCA (until June 30, 2018).
- Professor Jonathon Simon, DSc, MPH, Research Scientist, MCA.

On June 25, 2018, a consultation meeting was held with WHO at the PATH office in Geneva, Switzerland, to consider the first draft of this application. The key outcomes of that meeting are summarized in Annex II.

3. Organizations consulted and/or supporting the application

The following organizations were consulted in relation to this application. Those with an asterisk also provided a letter of support, included in Annex III. All organizations listed are partners or associates of the Diarrhea Innovations Group.

- Abt Associates, Washington, DC, USA*
- Aga Khan University, Karachi, Pakistan*
- Antara Global Health Advisors, Toronto, Canada
- Bill & Melinda Gates Foundation, Seattle, WA, USA*
- Clinton Health Access Initiative, Boston, MA, USA*
- ColaLife, London, United Kingdom
- Department for International Development, Glasgow, United Kingdom
- Ghana Health Services, Accra, Ghana*
- Institute for Health Metrics and Evaluation, Seattle, WA, USA*
- The Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, USA*
- Kintampo Health Research Centre, Kintampo, Ghana
- Ministry of Health, Zambia
- PanTheryx, Boulder, CO, USA
- PATH, Seattle, WA, USA
- Pharmanova Zambia, Ltd., Lusaka, Zambia*
- Senegal Ministry of Health and Social Welfare, Dakar, Senegal*
- United Nations Children's Fund, New York, NY, USA*
- Washington University, St. Louis, MO, USA

4. International Nonproprietary Names, Anatomical Therapeutic Chemical codes, and International Classification of Diseases classification

International Nonproprietary Names

Oral Rehydration Salts
Zinc sulfate

Anatomical Therapeutic Chemical codes

Oral rehydration salt formulation: A07CA
Zinc sulfate: A12CB01

International Classification of Diseases (ICD-11) classification

Diarrhea: ME05.1 Diarrhoea

5. Age-appropriate pediatric dose form(s) and strength(s) proposed for inclusion

a. Pediatric dosages for oral rehydration salts and zinc co-therapy

The co-package of ORS and zinc should contain the dose form and strength of ORS and zinc recommended for the treatment of a case of diarrhea in a child, which is detailed in the EMLc in sections 17.5.1 and 17.5.2 (Table 1). If these underlying recommendations were to change in the future, the changes would be reflected in the recommendation for co-packaged ORS and zinc.

Table 1. Current dose form and strength of oral rehydration salts and zinc for use in children.

17.5 Medicines used in diarrhoea	
17.5.1 Oral rehydration	
oral rehydration salts	**Powder for dilution** in 200 mL; 500 mL; 1 L. glucose: 75 mEq sodium: 75 mEq or mmol/L chloride: 65 mEq or mmol/L potassium: 20 mEq or mmol/L citrate: 10 mmol/L osmolarity: 245 mOsm/L glucose: 13.5 g/L sodium chloride: 2.6 g/L potassium chloride: 1.5 g/L trisodium citrate dihydrate*: 2.9 g/L * trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.
17.5.2 Medicines for diarrhoea	
zinc sulfate*	**Solid oral dosage form:** 20 mg. **[c]**. * In acute diarrhoea, zinc sulfate should be used as an adjunct to oral rehydration salts.

Source: World Health Organization (WHO). *WHO Model List of Essential Medicines for Children*. 6th List. Geneva: WHO; March 2017 (amended August 2017):31.

On this basis, the proposed co-package would contain:

- ORS (2 x 1 L sachets or 4 x 500 mL sachets or 4 to 6 x 200 mL sachets).
- Zinc (10 to 14 x 20 mg tablets).

b. A note on sachet size for oral rehydration salts

Bundling or co-packing of ORS and zinc is intended to encourage combined use of the products for the management of diarrhea in a single child. With this in mind, the smaller sachets of ORS (200 mL and 500 mL) are preferable. In most cases, a single child will not consume 1 L of fluid

within 24 hours, and after 24 hours any unconsumed solution should be discarded due to the high likelihood that it will be contaminated. This means that 1 L sachet sizes will result in a waste of safe water and ORS in most cases.

6. Listing requested as an individual medicine

This proposal requests the inclusion of co-packaged ORS and zinc as an additional single item under 17.5 (Medicines used in diarrhoea), as follows.

Table 2. Proposed listing for co-packaged oral rehydration salts and zinc sulfate.

17.5 Medicines used in diarrhoea	
oral rehydration salts* – zinc sulfate* **[c]**	**Powder for dilution** (see section 17.5.1) – **Solid oral dosage form** (see section 17.5.2) * Co-packaged for treatment of acute diarrhoea.
17.5.1 Oral rehydration	
oral rehydration salts	
17.5.2 Medicines for diarrhoea	
zinc sulfate	

Both ORS and zinc are currently on the core list of the WHO EMLc due to their lifesaving properties, public health relevance, and cost-effectiveness. For the current proposal, we request to retain these separate listings on the core list of the EMLc, while also including a new core listing of co-packaged ORS and zinc. Placement on the core list reflects co-administered ORS and zinc as a cornerstone of childhood diarrheal treatment worldwide and emphasizes the importance of both products as a basic minimum need for all health care systems treating the priority disease of diarrhea.

7. Treatment details (requirements for diagnosis, treatment, and monitoring)

a. References to current World Health Organization guidelines

Current WHO treatment guidelines for the management of childhood diarrhea (released in 2004) include the use of both ORS and zinc. There are numerous additional normative guidance documents from national and international associations that recommend or include the use of ORS and zinc as co-therapy for diarrhea, particularly in children less than 5 years of age. Annex IV includes a listing of relevant WHO guidelines.

b. Therapeutic dosage regimen and duration of treatment

The current WHO recommendations for ORS and zinc use in the management of diarrhea in children with **no** signs of dehydration are:

Low-osmolarity ORS (containing 75 mEq/L of sodium and 75 mmol/L of glucose)
After each loose motion:

- In a child younger than 2 years of age, provide 50 mL to 100 mL of ORS solution.
- In a child 2 to 10 years of age, provide 100 mL to 200 mL of ORS solution.
- In a child older than 10 years of age, provide ORS *ad libitum* (i.e., to drink freely).

Zinc sulfate
From the start of the diarrhea:

- In a child younger than 6 months, provide one-half of a 20 mg tablet (i.e., 10 mg) once a day for 10 to 14 days.
- In a child older than 6 months, provide one whole 20 mg tablet once a day for 10 to 14 days.

The ORS and zinc treatment plans above are described as Plan A in the WHO guidelines for treatment of diarrhea. Thus, according to the current WHO guidelines, **all** children with diarrhea who have no signs of dehydration should receive both ORS and zinc at the beginning of a bout of diarrhea. The duration of treatment with ORS and zinc differs, with OS provided only through resolution of diarrhea symptoms, while provision of zinc continuing for 10 to 14 days.

Treatment of diarrhea according to Plan A is appropriate for administration in the community by community health workers and caregivers in the home.

Plan B treatment for children with **some** dehydration also recommends both ORS and zinc administration. In Plan B, the zinc regimen is the same as for Plan A, but the guidance for low-osmolarity ORS is different. Instead of administering ORS according to loose motions (as in

Plan A), the ORS in the first 4 hours is administered according to the weight of the child (or the child's age if the weight is not known; Table 3).

Table 3. Dosages of oral rehydration salts according to a child's age and weight.

Age*	Up to 4 months	4 months up to 12 months	12 months up to 2 years	2 years up to 5 years
Weight	<6 kg	6 to <10 kg	10 to <12 kg	12 to 19 kg
In mL	200 to 400	400 to 700	700 to 900	900 to 1,400
*Use the child's age only when you do not know the weight. The approximate amount of ORS required (in mL) can also be calculated by multiplying the child's weight (in kg) by 75.				
- If the child wants more ORS than shown, give more.				
- For infants younger than 6 months who are not breastfed, also give 100–200 mL clean water during this period.				

The differing volumes of ORS recommended in Plan A and Plan B can be accommodated in a co-packaged kit of ORS and zinc, as the ORS sachets included are designed to prepare up to 2 L of ORS solution. A co-packaged kit of ORS and zinc would thus include instructions on how much ORS and zinc to administer and when to provide the doses of each, in accordance with WHO treatment guidelines.

Diagnosis, treatment, and monitoring of childhood diarrhea with ORS and zinc do not require specialized equipment, testing, or facilities. Diarrhea severity may be assessed through observation of the frequency and consistency of a child's stools, and dehydration is assessed through clinical signs and symptoms. Children with some dehydration should be assessed at least every 4 hours until the dehydration resolves. With simple health education, caregivers can be trained to recognize relevant symptoms and administer ORS and zinc in the home. Caregivers and community health workers can appropriately monitor children receiving ORS and zinc, assessing their recovery status and identifying cases that need more extensive treatment and/or hospitalization for severe cases.

The recommended treatment for children with severe dehydration is rapid intravenous rehydration—preferably while admitted to a hospital, where they can be reassessed every 15 to 30 minutes until a strong radial pulse is present; thereafter, they should be reassessed at least hourly to confirm that hydration is improving. All children with severe dehydration should receive ORS (about 5 mL/kg/h) once they can drink without difficulty (typically within 3 to 4 hours for infants or 1 to 2 hours for older patients).

Edematous (puffy) eyes are a sign of over hydration and indicate that ORS administration should be stopped. Once the edema has resolved, ORS administration can be resumed. The treatment of diarrhea in HIV-positive children is generally the same as in HIV-uninfected children, although lactose and monosaccharide intolerances are more frequently present in HIV-positive children. Assessment of dehydration is altered in children with severe malnutrition, as skin turgor, the appearance of sunken eyes, and irritability accompany marasmus and kwashiorkor. In severely malnourished children, it is often impossible to distinguish reliably between some dehydration and severe dehydration.

c. Implications for co-packaging

Co-packaged ORS and zinc should be used to support both treatment Plan A and treatment Plan B in the same way that ORS is used to support both treatment plans.

The current practice is to print Plan A instructions on ORS sachets and to identify dehydration as a danger sign requiring a visit to a clinic where an assessment can be made and Plan B can be initiated. The same approach should be taken with co-packaged ORS and zinc.

The guidance for zinc is the same for both treatment plans. It is current practice to print the instruction for the different dosing of zinc recommended for children younger than 6 months and older than 6 months of age on zinc sulfate packaging (i.e., 10 mg each day instead of 20 mg for older infants and children). The same approach should be taken with co-packaged ORS and zinc. As another option, manufacturers may consider developing separate co-packs targeted at infants younger than 6 months.

When co-packaging ORS and zinc, all ORS sachets must be from the same batch and therefore have the same expiry date. However, as the ORS and zinc sachets in a co-pack may have been produced at separate times, in many instances the zinc will have a different expiry date than the ORS. The expiry date of the co-pack must match the expiry date of the component within it that expires first.

8. Information supporting the public health relevance

a. Epidemiological information on diarrheal disease burden

Diarrhea is present globally, in all regions and among all populations. However, an inequitable proportion of diarrhea morbidity and mortality occurs in low-income countries, which in turn have fewer resources and less robust infrastructure to manage the burden.[15] The Global Burden of Disease Study (GBD) estimated diarrhea as the eighth leading cause of death, responsible for well more than 1.6 million deaths and the fifth leading cause of death among children younger than 5 years (446,000 deaths). Approximately 90% (89.37%) of diarrheal deaths occurred in South Asia and sub-Saharan Africa.[16,c]

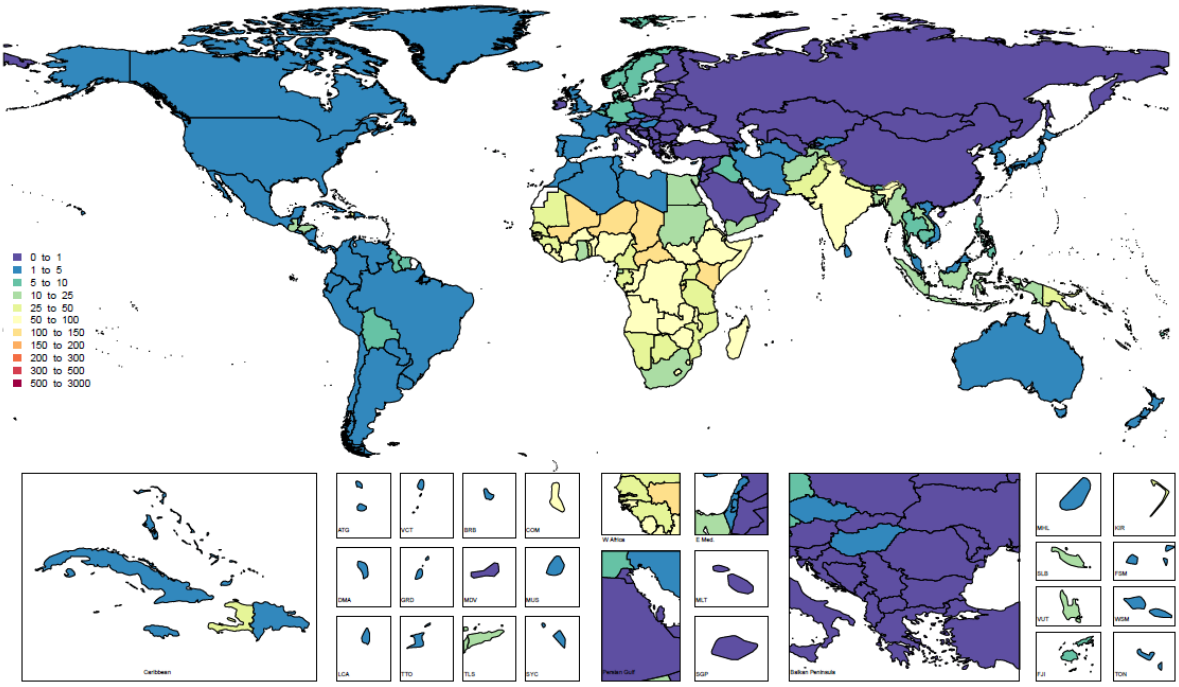
Estimates show that 2% of diarrhea episodes progress to severe cases, with approximately 72% of deaths in children younger than 5 years of age taking place within the first 2 years of life.[17] While the incidence of diarrhea peaks between 6 and 11 months, decreasing thereafter,[18] the proportion of deaths is greatest between 0 and 11 months, when the risk of disease and severity are at their peak.[17] Diarrheal diseases disproportionately affect locations with poor access to health care and safe water and sanitation, and in low-income or marginalized populations.[19] These observations illustrate that although challenges certainly exist, diarrhea mortality is largely avoidable and renewed efforts to reduce the burden of disease are urgently needed.

Overall, the diarrhea mortality rate according to the GBD is 22.4 deaths per 100,000 (Figure 1A below), with higher rates among children younger than 5 years (70.6/100,000; Figure 1B). The highest rates of diarrhea mortality among children younger than 5 years occurred in Chad (499 deaths per 100,000), the Central African Republic (384.2 deaths per 100,000), and Niger (376 deaths per 100,000) (Figure 1B).[16]

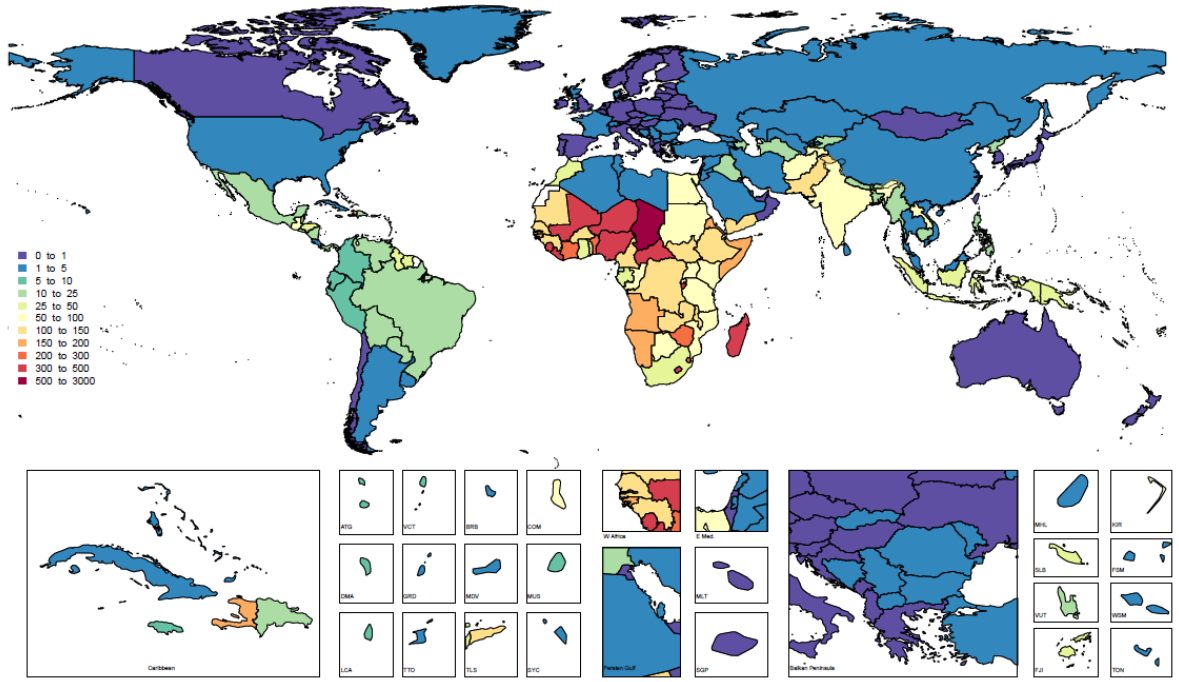
[c] Certain cross-cutting limitations of the GBD 2016 study that are applicable across many causes should be recognized. First, the newly developed data quality ratings by location do not incorporate the extent of redistribution for miscoded causes of death or other sources of error that might affect the accuracy of estimation based on those data. Second, both vital registration (VR) data and verbal autopsy (VA) data sources depend on how accurately underlying cause of death is assigned and this is complicated by multimorbidities. Third, in estimating fatal discontinuities for countries with a 3-star data quality rating or lower, the study primarily relied on international organisations that collate these data, and thus the results are subject to the limitations in data coverage or representativeness of those sources. Fourth, in adjusting VA studies relative to medical certification, the study relied on the single available study on this comparison; of necessity this is a limited basis for the adjustment. Fifth, sources of VA data vary substantially in terms of the training provided and the instrument used in collecting the data, which might reduce the comparability of cause of death data between locations. Sixth, the approach to garbage code redistribution is vital to the results presented in GBD 2016—although the methods of redistribution could theoretically contribute bias, the study has identified no evidence of this. Seventh, a low level of identified garbage coding for a given location does not necessarily indicate quality or accuracy in cause of death certification. Eighth, while some causes use negative binomial modelling approaches to improve estimation with over-dispersed data, the study has not yet developed a standardised empirical approach for selecting causes to use this method. Ninth, the study has not been able to systematically carry uncertainty from the statistical models used for many of the garbage code redistribution algorithms through to its final estimates due to limitations in computational requirements and storage needed. Tenth, additional sources of uncertainty might not be captured, such as for the covariates used in the models with the exception of the HIV crude death rate. Finally, GBD results are necessarily a combination of data and estimation. Due to lags in reporting, estimates for the most recent years rely more on the modelling process—evidenced by larger median UI by year between 2012 and 2016— as do estimates for locations with low levels of data completeness. For more information on limitations, please see pages 1201-1202 of the report (reference 16).

Figure 1. Maps of global diarrhea mortality rates for all ages (A) and children younger than 5 years (B).

(A) All ages diarrhea mortality rates in 2016.



(B) 2015 mortality rates for children younger than 5 years, both sexes combined.



Source: Institute for Health Metrics and Evaluation website. Data Visualizations. www.healthdata.org/results/data-visualizations. Accessed October 16, 2018.

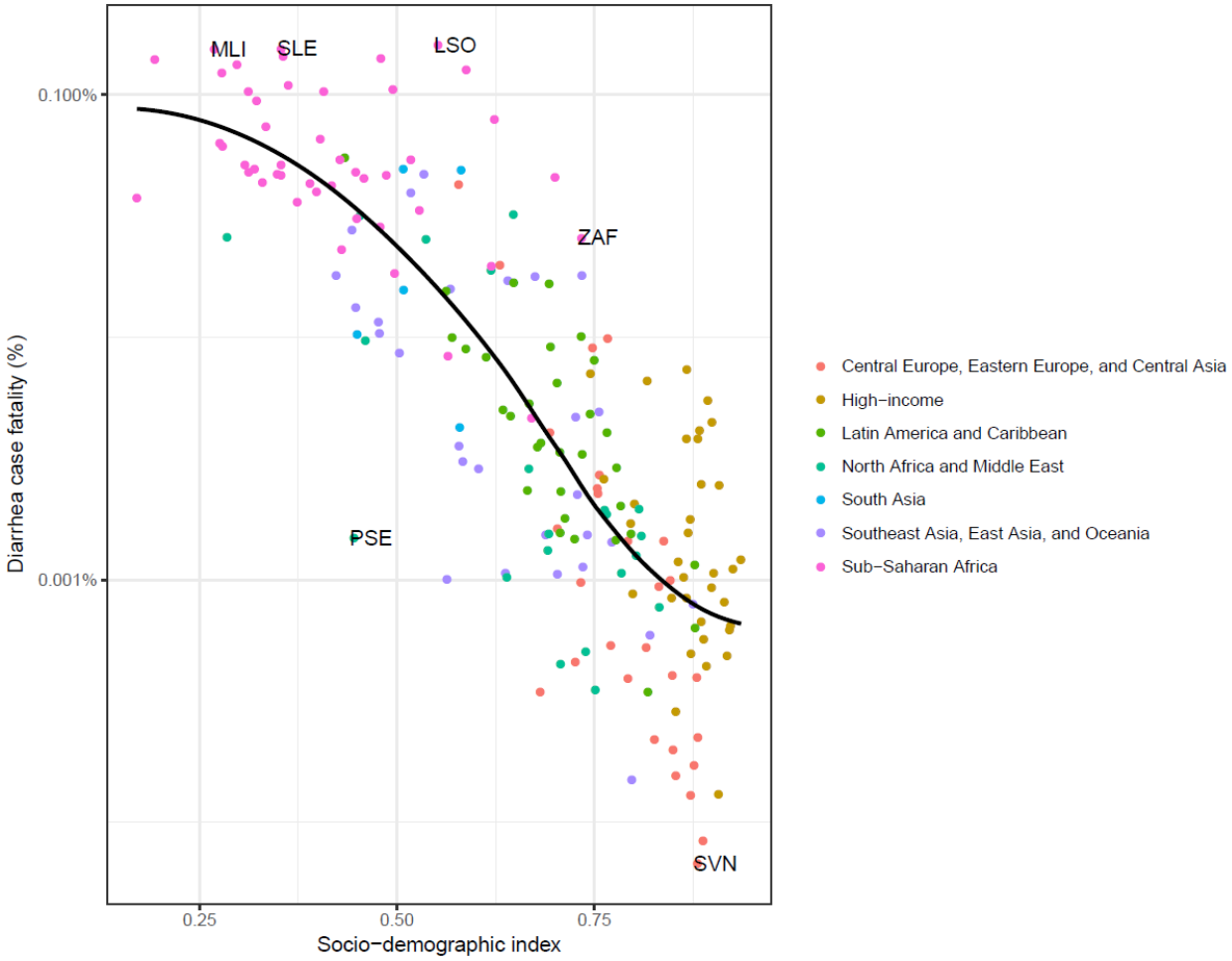
Diarrhea morbidity burden is also substantial; among children younger than 5 years, the GBD estimated 1.105 billion episodes of diarrhea in 2016 and 1.75 episodes per child in this age group. Diarrhea was the third leading cause of disability-adjusted life years (DALYs) in 2016, responsible for 74.4 million DALYs, 40.1 million (63%) of which occurred among children younger than 5 years of age. Diarrhea is among the most common reasons for hospital admissions of children in LMIC. It also accounts for a large proportion of case visits seen at rural health centers. In 2011, the greatest proportions of severe episodes of diarrhea occurred in the Southeast Asia (26%) and Africa (26%) regions. The highest numbers of deaths from diarrhea (about 50% of diarrheal deaths in 2011) occurred in sub-Saharan Africa.[17]

The case fatality ratio (CFR) of diarrhea quantifies the relationship between disease incidence and mortality. The CFR among children younger than 5 years decreases non-linearly with the Socio-demographic Index (SDI), a composite measure of fertility, education, and income (Figure 2 on the following page). The highest CFR among children younger than 5 occurred in western sub-Saharan Africa, where nearly 2/1,000 diarrhea episodes were fatal. Countries in southern sub-Saharan Africa, including Botswana, Lesotho, and South Africa, had higher CFRs than expected based on the SDI alone, perhaps due to the high HIV burden in these regions (Figure 2).[16]

The number of diarrhea deaths among children younger than 5 years of age has decreased dramatically since 2000, by 56.5%, and the diarrhea mortality rate in this age group has decreased by 59.3%. The incidence of diarrhea among children in this age group has also decreased, by 12.7% between 2000 and 2016.[16] Although diarrheal diseases have decreased dramatically in the last 3 decades, much work is still needed to accelerate burden reduction in the most vulnerable populations, including undernourished children, people lacking reliable access to safe water and sanitation, and those without access to appropriate health care.

Many countries achieved important successes in the fight against diarrheal diseases in the 1970s and 1980s, with the support of UNICEF and WHO through the National Control of Diarrheal Diseases Project.[20,21] For example, Egypt's program, which spanned from 1981 to 1991, was credited with significantly improving diarrheal case management using ORS.[22,23,24] However, over the last 2 decades, momentum has slowed.[25]

Figure 2. Case fatality rates and Socio-demographic Index plots for children younger than 5 years, 2016. The relationship between the Socio-demographic Index and the ratio of diarrhea deaths to incident cases (case fatality ratio) among children younger than 5, on a log10 scale, is shown. The black line shows a smoothed locally estimated scatterplot smoothing curve for this relationship.



Source: Institute for Health Metrics and Evaluation website. Data Visualizations. www.healthdata.org/results/data-visualizations. Accessed October 16, 2018.

Recognizing the magnitude of this burden, the global health community has made the prevention and treatment of diarrheal disease a priority. For example, in 2013 WHO and UNICEF coordinated the Diarrhea and Pneumonia Interventions Study Group, which developed the Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) and an accompanying series in *The Lancet*.[26,27] This plan established goals to reduce severe incidence of and deaths due to diarrhea in children by 2025. By promoting various effective interventions and 100 treatment strategies, the GAPPD targets mortality reductions to 1 in 1,000 and reductions in the incidence of severe diarrhea to 75% of the country-specific levels identified in 2010.

Regarding interventions for diarrheal disease, the use of ORS and proper nutrition are the second and third most efficient interventions globally. The relative order of efficiency among risk factors and interventions remains similar across diarrhea mortality rates. Six risk interventions (childhood wasting, unsafe water, not applying oral rehydration, unsafe sanitation, not applying handwashing, and non-use of therapeutic zinc) need to reach fewer than 3,000 children to avert a diarrhea death in sub-Saharan Africa.

b. Assessment of current use of oral rehydration salts and zinc in the treatment of diarrhea

In all, 14 years have passed since WHO and UNICEF released their joint statement[3] recommending low-osmolarity ORS and zinc supplementation for diarrhea treatment in 2004, yet even today, many children living in low-resource settings are not receiving these lifesaving interventions. ORS after each loose stool, until the diarrhea stops, and zinc supplementation for 10 to 14 days, are safe and effective in both home and facility settings when properly prepared and administered. Yet, of those children with acute diarrhea, a median of 42% receive ORS and less than 7% receive both ORS and zinc globally (with zinc tending to be the limiting factor).[4]

According to Fischer-Walker et al.,[28] many countries have been "stalled in the technicalities of adapting national policy for low-osmolarity ORS and zinc, while others struggle to find the funds for start-up activities." The problem is even worse in rural areas, where for millions of people, ORS and zinc are often not available locally and are hard to come by, either because of distance, cost, or stockouts of supply.[29,30]

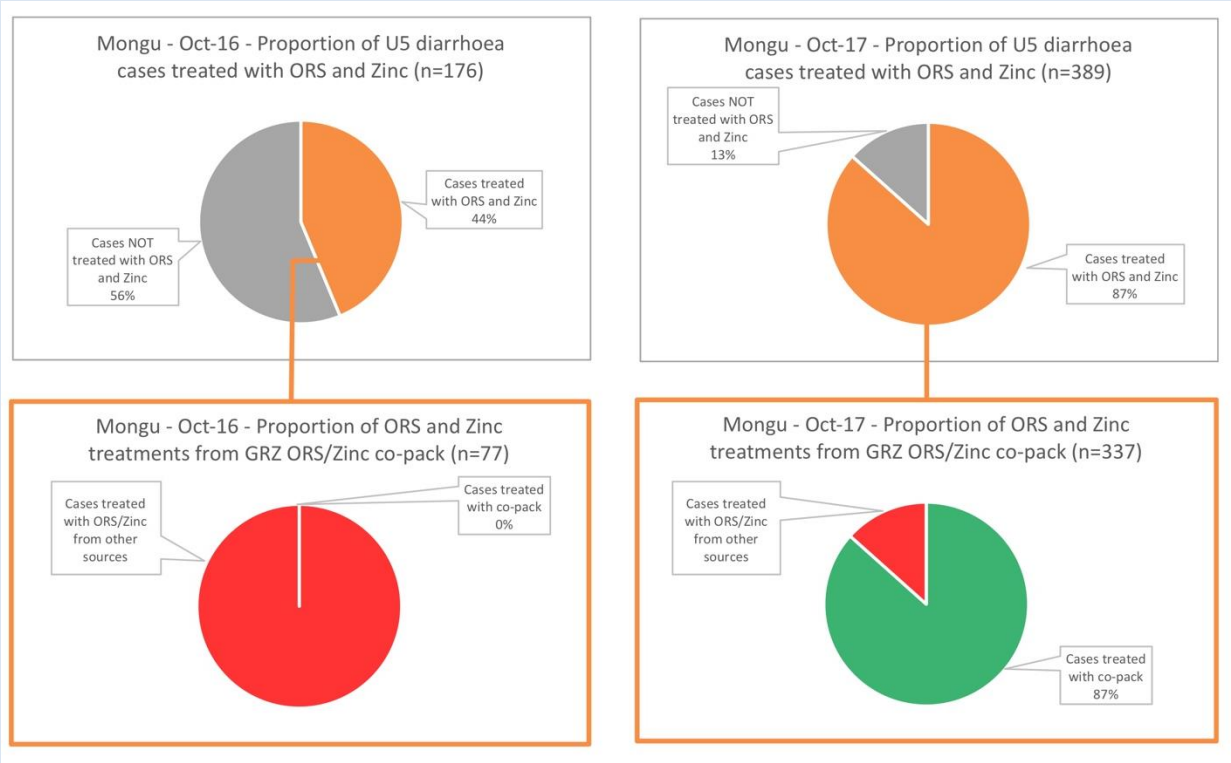
It has also been noted that providing ORS and zinc solely through public-sector clinics has not been effective, comprehensive, or sustainable in any country.[28] It has been suggested in recent calls for renewed action on ORS and zinc that the combined promotion of these two commodities is critical and may benefit from expansion to private-sector markets, social marketing, and targeted behavioral change campaigns.[26,28] Even though there were successes in the promotion of ORS in the early and mid-1980s, strategies currently being used by countries, if at all, are in need of renewal. Combined packaging and promotion of ORS and zinc may help address some of these shortfalls.

In addition, co-packaged ORS and zinc could offer significant utilization management and cost advantages for over-the-counter use and home treatment, as compared to separately packaged products. In fact, research studies in Ethiopia and Guatemala demonstrated that co-packaging ORS and zinc with instructions significantly improves adherence to treatment of diarrheal episodes at home.[31,32] Co-packaging also offers cost savings (see Table 7 in section 11), as promoting use of both ORS and zinc can bring down the overall cost of long-term health care and financial burden to families and communities[33] (see case study below).

THE CO-PACKAGING EFFECT – ZAMBIA CASE STUDY

The "co-packaging effect" was evident in a dispensing behaviors analysis conducted by ColaLife across eight health centers in Mongu District, Zambia, in October 2016 and October 2017. All eight centers had ORS and zinc in stock in October 2016; in addition, in October 2017, they all had co-packaged ORS and zinc. Before the introduction of co-packaged ORS and zinc in January 2017, the co-administration of ORS and zinc was already six times the global average, at 44% of childhood diarrhea cases treated with both ORS and zinc. However, this rate doubled to 87% when co-packaged ORS and zinc were made available (Figure 3).

Figure 3. Proportion of children younger than 5 years treated with both oral rehydration salts and zinc packaged separately versus co-packaged, Mongu District, Zambia.



When asked in December 2017, whether anything changed since receiving co-packaged ORS and zinc, and if so what, a district health director in Zambia replied:

> *Yes, what has changed is the availability especially of zinc, which is a part of [the co-pack] because I know previously we have never had problems with ORS availability but we have had problems when it came to zinc availability. But now that everything has been put into one kit, that has greatly improved the availability of zinc, which we know is important to limit the number of diarrhea cases and the duration of diarrhea. So the kit is really making an impact and* ***it also serves as a reminder for us, as we are prescribing as health workers, that we do not forget zinc being an important component in the treatment of diarrhea****.*

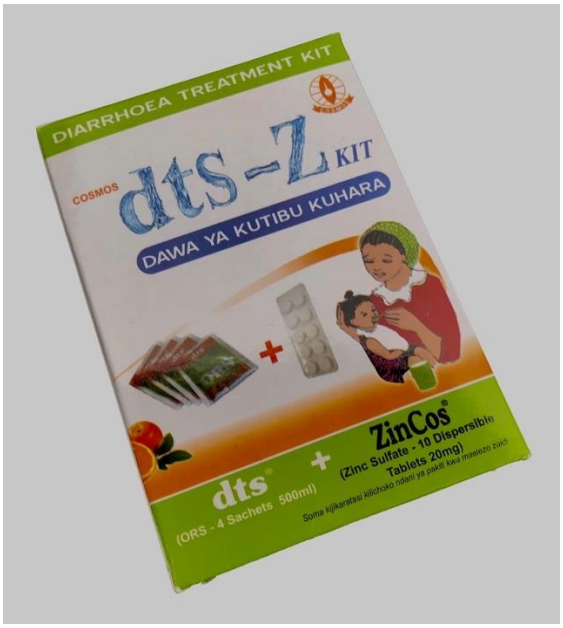
Despite the existence of these simple, inexpensive, and lifesaving treatments, access to ORS and zinc remains a challenge in low-resource settings, and the rate of co-administration is extremely low. The latest Countdown to 2030 report[34] found that of 43 countries with available data, median coverage of both ORS and zinc was 6% (range: 0% to 60%). The current WHO EML and EMLc list ORS and zinc separately, although they do specify under the zinc listing that "in acute diarrhoea, zinc sulfate should be used as an adjunct to oral rehydration salts."[1,2] Despite this instruction on joint administration, this only happens in a small minority of cases. In addition, the two products are treated very differently on NEMLs. A 2012 study, to examine the inclusion of these WHO priority medicines for maternal and child health on NEMLs, demonstrated that listed separately, ORS was on 93% (83/89) of lists, while zinc for diarrhea treatment in children was included on only 15% (13/89) of lists.[35] Another analysis, conducted by PATH in 2018, which reviewed 55 searchable NEMLs,[36] further demonstrated that only 47% (26/55) listed both ORS and zinc, and only 7% (4/55) listed both as a co-pack; 9% (5/55) did not list either ORS or zinc, 27% (15/55) listed ORS only, and 9% (5/55) listed zinc only (Table 4).

Table 4. Summary of oral rehydration salts and zinc listings on 69 national essential medicines lists.

ORS only (15 countries)	Algeria, Armenia, Bahrain, Barbados, Belize, Cambodia, China, Cook Islands, Indonesia, Malaysia, Mauritania, Myanmar, Timor-Leste, Togo, Zambia
Zinc only (5 countries)	Brazil, Chile, El Salvador, Mali, Republic of Congo
Neither ORS nor zinc (5 countries)	Cape Verde, Colombia, Côte d'Ivoire, Croatia, Lesotho
Both ORS and zinc, NOT co-pack (26 countries)	Afghanistan, Angola, Argentina, Bangladesh, Bolivia, Botswana, Burkina Faso,[a] Burundi, Cameroon, Central African Republic, Chad, Democratic Republic of the Congo, Eritrea,[b] Ethiopia, Guinea, India, Madagascar, Nepal,[c] Nigeria,[d] Pakistan,[e] Rwanda, Somalia, Sri Lanka, Sudan, Tanzania, Uganda
ORS/zinc co-pack (4 countries)	Ghana, Kenya, Senegal, Vietnam

[a] Does not specifically list co-pack, but does make a note: "En case de diarrhea aigue, le sulfate de zinc doit etre utilise comme adjuvant de la rehydratation orale chez l'enfant."
[b] Does not specifically note that medicines should be taken together, but they are listed together under "Medicines used in Diarrhoea." There is no indication they are listed as a co-pack.
[c] A note is made: "In acute diarrhoea, zinc sulfate should be used as an adjunct to oral rehydration salts."
[d] Does not specifically list co-pack, but does make a note in the NEML next to zinc that zinc "should be used as an adjunct to oral rehydration salts in acute diarrhea."
e A note is made: "In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts."

There are now several commercial co-packaged ORS and zinc products. A selection is shown below (see Annex V for more examples).

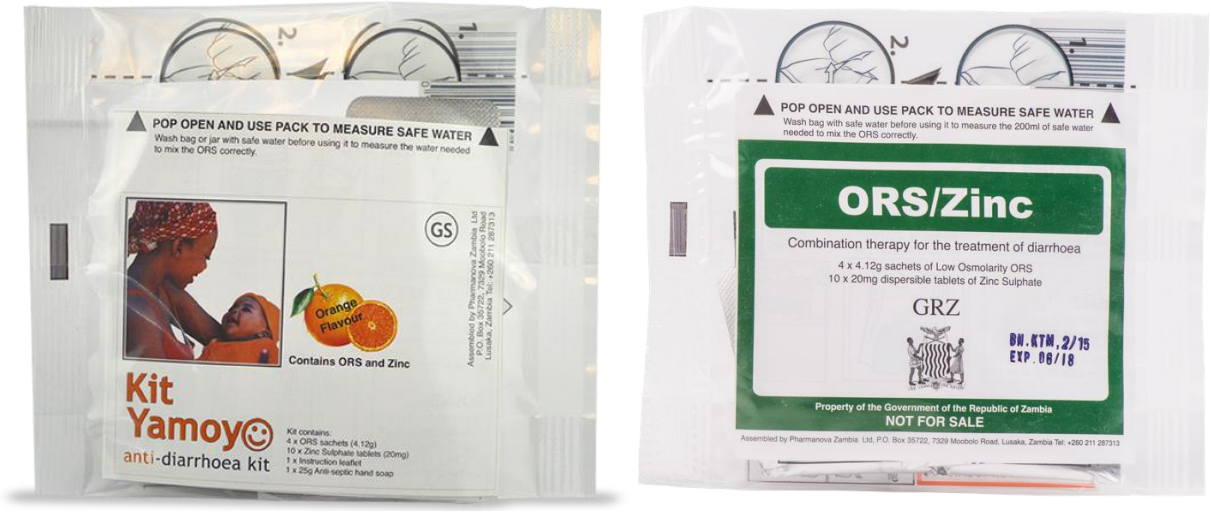


dts-Z Kit: Available in multiple countries, including Kenya and Uganda. Photo: ColaLife.

Orazinc Kit: Available in multiple countries, including Tanzania and Kenya. Photo: ColaLife.

The Kit Yamoyo anti-diarrhoea kit (Flexi-pack and Screw-top formats on supermarket shelves in Zambia. Photo: ColaLife.

In Zambia, a government-branded version of the commercial Kit Yamoyo product is produced for free distribution at health centers.



The commercially available Kit Yamoyo (left) and the government branded version (right). Photo: ColaLife.

The lack of a specific single listing for a co-packaged product creates a number of obstacles impeding access to this lifesaving therapy, including national-level policy and procurement challenges. It is clear from the experience of the last 14 years since the WHO/UNICEF diarrhea treatment recommendation was published, that while ORS and zinc are listed separately, they will tend to be procured separately, supplied separately, distributed separately, and dispensed together only in a small minority of cases. Today, less than 7% of diarrhea cases are treated with ORS and zinc.[34] Reasons include issues of inadequate stock of both products at the frontline at the same time, and lack of knowledge of global recommendations for diarrhea treatment or a

tendency, particularly in resource-poor settings, not to give "two medicines" (ORS and zinc) to treat a single case of diarrhea or to hold back zinc for cases judged to be "severe."

c. Target population(s)

All children with diarrhea.

d. Likely impact of treatment on the disease

Effects of co-packaging

Please see section 9 below for the effects of co-packaging.

Bhutta et al. modeled the benefits to the poorest quintiles associated with three strategies implemented through community-based platforms: scale-up of interventions for ORS and zinc; breastfeeding promotion; and case management of pneumonia. The results showed that if 90% coverage were achieved for these three interventions, 64% of diarrhea deaths could be averted in the poorest quintiles in the three countries assessed. As noted in a report of the study findings in *The Lancet*, titled "Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost?":[26]

> *Our findings show that several opportunities exist for scaling up the use of these interventions with community health-worker programmes, free distribution, social marketing, and co-packaging of zinc and oral rehydration solution, which can increase coverage by several times.*

This is in line with previous estimates, which demonstrated that more than three-quarters of diarrhea deaths could be prevented with full coverage and utilization of ORS and zinc.[37]

ORS-specific findings

Oral rehydration replaces lost fluids and essential salts, thereby preventing or treating dehydration and preventing the risk of death. Glucose contained in ORS enables the intestine to more effectively absorb the fluids and salts. Low-osmolarity ORS reduces the need for intravenous fluids (required in the most severe cases) and shortens the duration of diarrheal episodes.[38] Zinc supplementation is added to ORS as an adjunct therapy and has been proven to decrease the duration and severity of diarrheal episodes, as well as the risk of subsequent infections in the 2 to 3 months following treatment.[8]

Zinc-specific findings

Munos and colleagues assessed 157 LMIC studies to review the efficacy and effectiveness of ORS and found that it reduced diarrhea-specific mortality by 69%, and had a treatment failure rate of 0.2%.[6] Fischer-Walker and colleagues reviewed 13 zinc supplementation studies from

LMIC and concluded that zinc supplementation for diarrhea management was associated with a significant reduction of 46% in all-cause mortality and of 23% in diarrhea-related hospital admissions.[39]

9. Review of benefits: Summary of comparative effectiveness

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

While there is a significant amount of literature related to the combined use of ORS and zinc, we searched specifically for literature exploring aspects of co-packaging of ORS and zinc. The main focus was on whether, and to what extent, co-packaging can improve access to and rational use of the WHO and UNICEF global recommendation for the treatment of childhood diarrhea.

The search for evidence involved a review of published peer-reviewed journal articles and grey literature that explored various aspects of ORS and zinc co-packaging. The search was limited to English-language publications. Randomized, controlled trials, and quasi-experimental and observational studies were all eligible for inclusion in the review.

Key search terms: co-packaging, packaging, bundling, kit, ORS, zinc, diarrh(o)ea.

Databases searched: PubMed, Scopus, Popline, Google Scholar, Cochrane Library.

Cross-references and bibliographies of available data and publications were examined to identify additional sources of information.

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

A handful of geographically diverse individual studies to date have found significant public health benefits from introduction of co-packaged ORS and zinc (Table 5, beginning on page 26). These include:

- Increased uptake and coverage of ORS and zinc (as a combination therapy, and as individual components), reducing the risk of severe health consequences of chronic diarrhea and stunting, acute diarrhea, and zinc deficiency among children.
- Improved adherence to the combined therapy of ORS and zinc.
- Improved adherence to/preparation of individual components (e.g., correct concentration of prepared ORS and completion of a full course of zinc).
- Improved dispensing practices by health care workers.
- Reduced hospitalizations due to diarrhea.
- Reductions in inappropriate antibiotic prescription and use.
- Enhanced satisfaction levels by caregivers with ORS and zinc relative to status quo products.

- Enhanced opportunities for developing private-sector models and leveraging value chains to improve availability and access closer to the household level.

In addition, this inclusion could facilitate a number of normative and other benefits, such as:

- **A cascade effect.** Global treatment guidelines and the essential medicines listings serve as important guides for countries in their development of NEMLs and procurement and supply of medicines for donation and local medicine production, as well as training of health care providers.[12,13] Listing of co-packaged ORS and zinc has the potential to foster an enabling environment for country-level policy work to prioritize access to treatment and incorporate co-packaged ORS and zinc into national health programs.
- **An awareness effect.** WHO EML listing stands to increase recognition and reinforcement among policymakers and health care professionals of co-administered ORS and zinc as a cornerstone of childhood diarrheal treatment worldwide.
- **Availability effect.** Listing of a co-packaged product can guide the selection, procurement, and supply of medicines in the public sector, schemes that reimburse medicine costs, and medicine donations, from the national level down to provincial/regional and district levels within countries.[14]
- **A manufacturer effect.** The listing may catalyze increased demand and spur local medicine production, with manufacturers responding and creating more market competition.[12]

While a number of systematic reviews explore the benefits of combined ORS and zinc use for childhood diarrhea, there are no systematic reviews exploring the benefits of ORS and zinc co-packaging specifically. Ample anecdotal evidence is also beginning to emerge from countries that have introduced co-packaged ORS and zinc, supporting the findings above.[40,41] Lenters et al.[42] conducted a systematic review, published in 2013, of peer-reviewed and grey literature to explore strategies to increase use of ORS at the household level. A range of intervention categories was found, including co-packaging of ORS and zinc. However, meta-analysis for this intervention category was found not to be possible due to the limited number of studies. All studies on the topic since this review are included in Table 5 below.

Table 5. Summary of evidence.

Patients	Intervention	Impact
Borapich D. et. al., 2010[43] Cambodia		
A total of 77 focus group discussions with caregivers in rural Cambodia and a mid-term household survey conducted by the Red Cross (details not publicly available).	Population Services International/ Cambodia implemented a pilot project to promote and distribute a diarrhea treatment kit (DTK) branded Orasel KIT, including low-osmolarity ORS sachets, one blister pack of ten tablets of 20 mg dispersible zinc, and an instructional leaflet. The project was launched in selected districts of Siem Reap and Pursat. The product was distributed through commercial	Evaluations of the project (despite being mainly qualitative and including a small household survey) suggest the program was effective in increasing the use of combined ORS and zinc, particularly among low-income rural and semi-urban populations. Results suggested a high level of support for and satisfaction with the DTK among stakeholders, providers, and caregivers. Overall, use of ORS and associated diarrhea treatment behaviors increased over time, and ORS and zinc recognition and ORS use were

Patients	Intervention	Impact
	retail outlets, village shopkeeper networks, and community health workers. A communication campaign targeted caregivers of children less than 5 years of age, promoting the Orasel KIT and its use through mass media, a mobile video unit, interpersonal communication, and promotional materials.	higher among implementation (DTK) villages than comparison villages. The pilot project demonstrated that a DTK is an acceptable product to caregivers, that diverse communication approaches can increase awareness and use of the product, and that using private provider networks can successfully improve availability of the product. The Ministry of Health viewed the DTK as an opportunity to train staff, and felt that it provided an added incentive. They also felt that the DTK was affordable and made effective diarrhea treatment more readily available to caregivers. Medical providers felt the Orasel KIT was preferable to existing options. Caregivers believed that the DTK tasted good and was effective in stopping diarrhea in 2 to 3 days, with children showing improved skin pallor and appetite. They also felt that the price of the Orasel KIT was reasonable and preferred that the products be packaged and sold together. Co-packaging is an effective means of marketing these products and encouraging their combined use.
Gebremedhin S. et al., 2016[32] Ethiopia		
In each of the four arms, 176 children 6–59 months of age who presented with acute diarrhea were enrolled.	This study evaluated whether co-packaging using a plastic pouch could enhance joint adherence to the treatment. The primary objective was to determine the level of joint adherence to ORS and zinc treatment; secondarily, the study looked at adherence to ORS and zinc treatment separately. The study also compared the cost-effectiveness of two co-packaging options: central- and health center–level bundling. A cluster-randomized, controlled trial was conducted in eight districts of Ethiopia, in which 32 health centers were randomly assigned to one of the following four intervention arms: 1. Central bundling (ORS and zinc bundled using a pouch that had an instructional message, distributed to health centers).	*Adherence to combined therapy:* The joint adherence level in the central- (86.4%) and health center–level (86.5%) bundling arms was comparable and significantly higher than the level in the other two arms (bundling without message [74.1%] and status quo [71.6%]). As compared with the status quo arm, joint adherence to ORS and zinc in the central- and health center–level intervention groups increased significantly, by 14.8 and 15.7 percentage points respectively ($p<0.001$). *Adherence to zinc:* In the status quo arm, only 37.9% of the children received the full 10 days of zinc. The corresponding figures for the bundling without message, health center–level bundling, and central bundling were 45.7%, 64.6%, and 65.9%, respectively. Relative to the average number of tablets given across all four arms (7.7 ± 2.90), adherence levels were significantly higher in the health center–level bundling (8.55 ± 2.31) and central bundling (8.50 ± 2.56) groups and lower in the bundling without message (7.23 ± 3.19) and status quo (6.70 ± 3.36) arms ($p<0.001$).

Patients	Intervention	Impact
	2. Health center–level bundling (ORS, zinc, and a similar pouch distributed to health centers and bundled by health workers). 3. Bundling without message (ORS, zinc, and a plain pouch distributed and bundled by health workers). 4. Status quo (ORS and zinc co-administered without bundling). Level of adherence was assessed 12 days (median) after enrollment.	*Adherence to ORS:* About 63.9% of the respondents in the status quo arm reported that they provided ORS every time after an episode, as recommended. The corresponding figures for the bundling without message, central-level bundling, and health center–level bundling were 64.2%, 79%, and 80.5%, respectively. Overall, the average adherence levels for ORS treatment in the four arms (i.e., proportion of diarrheal episodes followed by ORS administration) were health center–level bundling, 87.8%; central-level bundling, 87.5%; status quo, 76.1%; and bundling without message, 76%. Compared with the other two groups, the central- and health center–level bundling interventions increased ORS adherence by 10.2 to 12 percentage points ($p<0.05$).
Roche M. et al., 2015[31] Guatemala		
Two arms, an intervention group (n=123) and a control group (n=138).	This study evaluated the effectiveness of health facility–level co-packaging of ORS and zinc in improving health provider prescription practices and caregivers' adherence to the diarrhea treatment for children 2 to 59 months of age in rural Guatemala. ORS co-packaging development was guided by social marketing and then evaluated in a community-randomized intervention trial. The intervention group received ORS and zinc in a graphic co-pack with instructions and provider messages for counseling on diarrhea treatment. The control received normative care with ORS and zinc without co-packaging or messages. Home monitoring of adherence was conducted at 5 and 10 days post-prescription in 20 health posts in San Marcos Province.	Health providers in the intervention group were more likely to dispense both medications than those of the control group (adjusted odds ratio [aOR]: 2.3; 95% confidence interval [CI]: 1.0, 5.4). Intervention group mothers were more likely to give the full 10 days of zinc (aOR: 1.7; 95% CI: 1.0, 2.8) than control group mothers, and intervention mothers provided 1 more day of zinc ($p<0.01$). Co-packaging improved both prescription practices and adherence to zinc.
Habib M.A. et al., 2013[44] Pakistan		
Nearly 26,000 households were visited during the baseline, 13,871 in the intervention areas and 12,092 in the control areas. The survey identified 14,418 children less than 5 years of age in the	A cluster-randomized trial with eight clusters, four intervention and four control. A baseline survey was conducted in all clusters, followed by the delivery of a diarrhea treatment pack containing two packets of low-osmolality ORS, one strip of ten zinc tablets, two water purification sachets, and one informational leaflet) in the	Results showed a significant increase in uptake of ORS and zinc along with a reduction in antibiotic use, diarrhea burden, and hospitalization in the intervention clusters as compared to the control clusters. The diarrhea treatment pack components were well accepted in the community. In round one, ORS use was 66.5% versus 26.3%; in round two, ORS use was 82.2%

Patients	Intervention	Impact
intervention areas and 16,204 in the control areas.	intervention clusters through community health workers at domiciliary level and through sales promoters to health care providers and pharmacies. Four quarterly surveillance rounds were conducted to evaluate the impact of the diarrhea treatment pack in all clusters by an independent team of field workers.	versus 20.8%; in round three, ORS use was 89% versus 27%; and in round four, ORS use was 84.3% versus 28.4% among the intervention and control groups, respectively. A significant difference was also established in all four rounds. Utilization of zinc in rounds one, two, three, and four in the intervention clusters was 68.5%, 85.5%, 91.8%, and 87.3%, respectively; while in the control clusters, the utilization of zinc was found to be much lower: 26.2%, 20.5%, 27.3%, and 28.7%, respectively. The results revealed significant differences in utilization of zinc in the intervention and control clusters. Overall, after introduction of the co-pack, ORS use was 80.9% (95% CI: 68.5-93.2) in the intervention clusters and 25.7% (95% CI: 15.8-35.6) in the control clusters, and zinc use was 83.3% (95% CI: 73.2-93.3) in the intervention clusters and 25.6% (95% CI: 15.8-35.5) in the control clusters. Antibiotic use decreased, and was 8.9% (95% CI: 5.2-12.7) in the intervention clusters and 38.8% (95% CI: 32.1-45.4) in the control clusters.
Ramchandani R., 2016[33] (manuscript currently under review by *The Lancet Global Health*) Zambia		
A quasi-experimental pre-/post-test design in two intervention districts of rural Zambia, each with a matched comparator, assessed the intervention's effect on coverage of (1) ORS and zinc and (2) ORS with or without zinc by conducting household surveys of 2,458 and 2,477 caregivers of children younger than 5 years at baseline and endline, respectively.	Market-based approaches of commercial value chains of fast-moving consumer goods, both the supply and demand sides, were adopted and lessons applied to the introduction of an innovative DTK. The kit contained four 200 mL sachets of low-osmolarity ORS, a blister pack of ten 20 mg tablets of zinc, a small bar of hand soap, and an instructional pamphlet. Kits were sold at the community level through small, local, private-sector retailers.	Use of ORS and zinc combination therapy increased from less than 1% to 46.6% across the intervention districts, while comparator districts demonstrated no change (pooled risk ratio: 39; 95% CI: 13.2-115.2; p<0.001). Difference-in-differences analysis comparing ORS use (with or without zinc) in intervention and comparison districts, before and after market-shaping activities, found that ORS use increased significantly across the intervention districts, from 59.8% to 76.4% (odds ratio [OR]: 2.17; 95% CI: 1.47-3.24; p<0.001), while usage across comparators decreased non-significantly, from 66.4% to 58.2% (OR: 0.71; 95% CI: 0.48-1.04; p<0.08). The proportion of ORS users sourcing public-sector ORS fell from almost 100% to 40.1% (Kalomo) and 34.1% (Katete), while in comparator districts, ORS continued to be sourced solely from the public sector. Implementation of a value chain approach for an innovative, over-the-counter DTK can significantly improve co-packaged ORS and zinc coverage at the community level.
Progress over a Decade of Zinc and ORS Scale-up: Best Practices and Lessons Learned[40]		
NA.	In Kenya, the Clinton Health Access Initiative (CHAI) worked	Public-sector volumes for ORS and zinc treatment courses (including new co-pack

Patients	Intervention	Impact
	with Ministry of Health (MOH) facilities to bundle existing singles into re-sealable zipper storage bags to introduce the co-package concept to health facilities and draw down existing singles stock. CHAI then analyzed Kenya's procurement volumes from 2013 to 2016.	products) have grown by more than 35% since 2013.

Recommendations related to co-packaging of oral rehydration salts and zinc

While numerous recommendations have been developed for ORS and zinc as individual treatments and as combination therapy for the treatment of childhood diarrhea (see Annex IV), WHO has not developed any formal recommendations related to co-packaging specifically. Nonetheless, considerable guidance, as well as commentary on the promise of co-packaging, has been provided by WHO and key partners, including the following:

WHO and UNICEF's landmark publication *Diarrhoea: Why Children Are Still Dying and What Can be Done*[45] notes:

- *Possible strategies to increase their [ORS and zinc] uptake and availability could include the development of smaller ORS packets and flavoured formulas, as well as delivering zinc and low-osmolarity ORS together in diarrhoea treatment kits.*
- *Clear policy guidance is needed to ensure that the latest recommendations for treating childhood diarrhoea are adopted and promoted, using effective delivery strategies. One way of facilitating the delivery of low-osmolarity ORS and zinc is by combining these life-saving remedies in a single treatment kit.*
- *Products need to be delivered in innovative ways that maximize access. ORS packets and zinc could reach more children in need if packaged together in diarrhoea treatment kits, which could be delivered by community health workers, or directly to households through campaigns or Child Health Days. Pregnant women could also receive such kits during antenatal care visits.*

WHO guidelines for policymakers and program managers for *Implementing the New Recommendations on the Clinical Management of Diarrhoea*[46] note:

- *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.*

Other key guidance related to co-packaging has been summarized in the recent Diarrhoea and Pneumonia Working Group paper *Progress over a Decade of Zinc and ORS Scale-up: Best Practices and Lessons Learned*:[40]

- *Introducing a zinc/ORS co-pack (multiple ORS sachets and a 10-day course of zinc tablets) has been an effective strategy for improving uptake in the public sector, when certain conditions were in place:*
  - *A local assessment to determine the potential need and impact of co-pack introduction*
  - *A cheaper co-pack price compared to the combined cost of single products*
  - *A clear [ministry of health] strategy to manage product transitions, including communication on any change in pack size and order requirements as well as key messages highlighting the rationale for the product switch*
  - *Favorable policies (e.g., [over-the-counter] status secured for both zinc and ORS)*
  - *Product "bundling" of single units (with close monitoring of expiration dates for both products) prior to the switch to sensitize pharmacies and clinicians*
  - *Buy-in secured from relevant [health ministry] departments (e.g., Child Health, [National Medical Stores])*
- Guidance on product optimization and cross-cutting recommendations included:
  - *Smaller ORS sachet sizes to eliminate wastage of ORS and water and reduce contamination risk*
  - *Flavored ORS and taste-masked zinc for improved palatability*
  - *More attractive pack designs to increase caregiver appeal*
  - *Kit packaging that can double as a measurement vessel*
  - *Pictorial dosing instructions to facilitate correct dosing, mixing, and administration*
  - *Co-packaged zinc and ORS to encourage purchase and use of products together*

Finally, also worth highlighting is UNICEF's Suppliers and Product Range for ORS and zinc, which notes:[47]

- *In order to improve compliance, manufacturers have co-packed ORS and zinc in accordance with [WHO] treatment protocol guidelines to improve treatment regimen adherence.*
- *UNICEF is supporting governments to scale-up the use of ORS and zinc by sourcing and promoting quality co-packaged ORS and zinc in order to facilitate access in countries requiring secure and stable programme supply.* This includes *introducing at scale the innovative co-packaged ORS and zinc through the public sector*.
- *Providing ORS and zinc as co-packaged products will ensure that caregivers dispense, and patients adhere, to current recommended treatment for childhood diarrhoea. Co-packaged ORS and zinc availability through the public sector is a priority and since the introduction of ORS and zinc co-packaged products into UNICEF's Supply Catalogue in 2014, sixteen countries have introduced this product for public sector distribution*.

c. Summary of available estimates of comparative effectiveness

All of the studies summarized in Table 5 compare co-packaged ORS and zinc to a counterfactual of ORS and zinc provided separately. Based on our review, these are the only studies available that provide comparative effectiveness of co-packaged ORS and zinc to the majority situation of ORS and zinc being provided separately. Findings from these studies, including that increases in

uptake of ORS and zinc combination therapy ranged from 15% to 62%, support the recommendation for inclusion of a co-packaged product on the WHO EMLc.

10. Review of harms and toxicity: Summary of evidence of safety

a. Estimate of total patient exposure to date

Published literature supports the safety and effectiveness of ORS dating back more than fifty years, and for zinc over the last thirty. For more than 25 years, WHO and UNICEF have recommended a single formulation of glucose-based ORS to prevent or treat dehydration from diarrhea irrespective of the cause or age group affected. This product has contributed substantially to the dramatic global reduction in mortality from diarrheal disease during this period, with ORS being hailed as "potentially the most important medical advance of this century."[48] In addition, the 2004 WHO/UNICEF joint statement recommends a new lower-osmolarity ORS formulation and zinc supplementation for diarrhea management.[3] Since then, ORS and zinc have been used to treat acute and persistent diarrhea. Globally, there are nearly 1.7 billion cases of diarrheal disease annually.[47] It is estimated that a median of 42% of children suffering from diarrhea are treated with ORS and a median of 7% with both ORS and zinc.[4] Although significant challenges contribute to limited availability and utilization of ORS and zinc in many countries, use is increasing but is still at unacceptably low levels as above. UNICEF alone procures approximately 55 million ORS sachets a year, though volumes can range from 30 million to 80 million sachets per year depending on emergency response. UNICEF's procurement of zinc has steadily increased over the past 10 years to reach 350 million tablets in 2014, from 20 million in 2005. UNICEF began procuring co-packaged ORS and zinc in 2014, and to date the number has reached 7.8 million co-packs.[477]

b. Description of adverse effects/reactions and estimates of frequency

Studies demonstrated the 245 mOsm/L solution appeared to be as safe and at least as effective as standard ORS (311 mOsm/L) for use in children with cholera. However, the reduced-osmolarity ORS containing 75 mEq/L sodium, 75 mmol/L glucose (total osmolarity of 245 mOsm/L) is associated with an increased incidence of transient, asymptomatic hyponatremia in adults.[49] In a large phase 4 study in 53,280 patients at the Dhaka hospital and Matlab hospital of icddr,b, the incidence rate of hyponatremia was 0.05% (95% CI: 0.03%-0.07%) and 0.03% (95% CI: 0.01%-0.09%) respectively.[50] This reduced-osmolarity ORS may be used in place of standard ORS for treating adults with cholera, but careful monitoring is advised to better assess the risk, if any, of symptomatic hyponatremia.

Overall, ORS is safe, with few reports of adverse events. Additional adverse events that occur with ORS administration include edematous (puffy) eyelids, which are a sign of over hydration,[51] and vomiting. Vomiting often occurs within the first 1 to 2 hours of treatment, especially when children drink the solution too quickly, but this rarely prevents successful oral rehydration since most of the fluid is absorbed.

Oral zinc supplements can cause side effects such as stomach upset, heartburn, and nausea. Rare side effects include fever, sore throat, mouth sores, weakness, and fatigue.[52] In addition, large doses of zinc for long periods can interfere with metabolism of other minerals, including iron, magnesium, and copper. Copper deficiency can subsequently result in anemia. Although zinc-induced copper deficiency and the resulting anemia can be serious, it only occurs after excessive zinc intake over a long period and can be treated by adjusting the intake of zinc and copper accordingly.[53] Zinc supplementation can also compete with absorption of iron. There are a number of reported cases of adverse effects due to excessive zinc intake, the majority involving adults who knowingly ingested many times the normal daily dose of zinc over a long period. Even in the most extreme cases (more than 1 g/day for many months), patients recovered from all signs and symptoms, including fatigue, gastrointestinal discomfort, and anemia, when zinc intake was decreased and serum zinc returned to the normal range.

Zinc supplementation has been utilized extensively with demonstrated safety in the treatment of diarrhea. To date, there have been no reports of severe adverse reactions from any form of zinc treatment for diarrhea,[533] alone or in combination with ORS. Short-course supplementation trials included more than 9,100 children who 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. No differences in adverse reactions were found based on the different zinc salts used in the supplementation trials (i.e., sulfate, acetate, and gluconate). The only reported side effect of zinc supplementation in these studies was vomiting.[533] In a meta-analysis of 11 acute diarrhea studies (N=4,438), 12.7% of study participants vomited after the initial dose of zinc compared to 7.6% after placebo (risk ratio: 1.55; 95% CI: 1.30-1.84; $p<0.001$).[54] In three studies evaluating copper, no difference in serum copper was found after zinc supplementation.[9,55,56] In another study, a significant trend toward lower copper status was found in zinc-treated compared to untreated children.[57] Overall, there is no substantial evidence that short-term zinc administration for the treatment of diarrhea adversely affects copper status. Lastly, in preclinical safety studies, zinc has been shown not to be carcinogenic, mutagenic, or teratogenic.[58]

c. Summary of available data

The overall safety profile of ORS and zinc and reported adverse events represents a long history of use in clinical practice for the treatment of diarrhea. Given the proven efficacy and safety of ORS and zinc, these treatments continue to be widely used for management of patients with diarrhea. WHO recommendations on the clinical use of ORS and zinc have been published based on evidence and expert consensus. ORS and zinc continue to be widely used for management of acute and persistent diarrhea because of the favorable therapeutic index and benefits that outweigh the risks. Many studies that evaluated the safety and efficacy of ORS and zinc were randomized, prospective studies. In addition, clear recommendations on the use of ORS together with zinc are found in the standard integrated management of childhood illness guidelines and are included in WHO's EML,[1] and on the list of Priority Medicines for Mothers and Children,[59]

as well as NEMLs and treatment guidelines for childhood diarrhea treatment in many high-burden countries.

Zinc supplementation is a safe and effective treatment for diarrhea. Zinc has also been shown to be safe in long-term supplementation studies. The most severe adverse effects noted in supplementation trials have been vomiting in some cases and a slight reduction in copper status in some children. Neither has been shown to cause any long-term harm. Although there have been case reports in adults of excessive zinc intake, the adverse effects even in these cases have been limited to short-term morbidity, and few have resulted in any long-term sequelae.

d. Summary of comparative safety against comparators

According to WHO, the mainstay of acute diarrhea treatment is the prevention of dehydration with adequate liquids, ORS, zinc supplementation, and maintenance of oral feeding.[511] In addition to the glucose-based ORS described within this application, studies have been conducted since 1980 to evaluate a rice-based ORS as an alternative to a glucose-based ORS. Based on a Cochrane systematic review, there was no statistically significant difference between the rice-based and glucose-based ORS groups in the number of participants who developed vomiting (10 trials, 584 participants), hyponatremia (4 trials, 385 participants,), hypokalemia (2 trials, 260 participants), or persistent diarrhea (2 trials, 885 participants).[60] WHO currently recommends a reduced-osmolarity ORS, although studies have demonstrated that participants who received reduced-osmolarity ORS developed an increased risk of hyponatremia after 24 hours of treatment, defined as a serum sodium concentration of less than 130 mEq/L (29 patients treated with reduced-osmolarity ORS developed hyponatremia versus only 16 in the group treated with standard ORS; odds ratio: 2.1; 95% CI: 1.1-4.1).[38] However, the proportion of patients with serum sodium of less than 125 mEq/L 24 hours after initiation of treatment was similar in the two groups. No patient had symptoms due to hyponatremia.

Antibiotics may be appropriately recommended for cholera and dysentery diarrhea, but are not recommended for all forms of diarrhea. For dysentery or cholera, treatment with ORS and zinc is not meant to replace antibiotic treatment, but can be given in addition to antibiotic therapy. For episodes that do not require the use of antibiotics, the need is great for alternatives to discourage the inappropriate use of antibiotics for effective antibiotic stewardship.

Anti-diarrheal drugs are not recommended for acute diarrhea in children[511] and can have safety concerns. Antimotility drugs (e.g., loperamide hydrochloride, diphenoxylate with atropine, tincture of opium, camphorated tincture of opium, paregoric, codeine) may reduce the frequency of stool passage in adults; however, they do not appreciably decrease the volume of stool in young children. Moreover, they can cause severe paralytic ileus, which can be fatal, and they may prolong infection by delaying elimination of the causative organisms. Sedation may occur at usual therapeutic doses and fatal central nervous system toxicity has been reported for some agents. None of these agents are recommended to be given to infants or children with diarrhea.

e. Identification of variation in safety that may relate to health systems and patient factors

ORS and zinc have been evaluated in a variety of settings, including inpatient hospitals, outpatient facilities, and community settings. There has been no variation in safety due to differences in persons administering the supplement or differences in setting. Data also support ORS and zinc safety for the treatment of diarrhea in children across the age range. Studies evaluating ORS and zinc in low-resource settings included children of varying nutritional status. One meta-analysis showed no difference in safety of zinc when stratified by nutritional status.[8]

Treatment of children with diarrhea should be evaluated during rehydration to ensure that ORS solution is being taken correctly and that signs of dehydration are not worsening. Insufficient education and training including lack of familiarity with ORS and zinc may relate to variations in safety and efficacy of ORS and zinc administration that differ across settings and populations. Programs aiming to scale up zinc treatment for childhood diarrhea should train providers to successfully communicate dosing instructions to caregivers. In studies assessing adherence to the zinc dose and duration of supplementation demonstrate the importance of education. A randomized, controlled trial in Bangladesh reported that on average children with diarrhea received only 7 days of the total 14-day zinc dosage.[61] In addition, monitoring adherence to dosage instructions is important, as administration of higher doses of zinc may increase toxicity.

Another contributing factor is caregiver perception. In a study evaluating adherence to guidelines for the treatment of diarrhea, zinc was not frequently reported as the preferred treatment by caregivers (29.2%), as compared to reports from caregivers of treatment with ORS (58.4%), syrups (81.4%), and tablets (92%). The proportion of providers who advised continuation of zinc for 14 days (85.8%) was higher than the proportion who advised the age-appropriate dose (63.7%). In addition, a higher proportion of providers offered correct dosage instructions for zinc tablets than for zinc syrups. This study observed the opposite trend among caregivers, for whom adherence to provider instructions on the 14-day duration of zinc treatment (52.6%) was lower than adherence to the age-appropriate dose (87.5%).[62] This finding suggests that zinc adherence challenges are different for providers and caregivers and thus critical to future program planning.

Lastly, to ensure safety, both ORS and zinc should be manufactured only by licensed manufacturers that meet Good Manufacturing Practice standards.

11. Summary of available data on comparative cost and cost-savings of the medicine

The table below provides illustrative data from Ghana, Kenya, Nigeria, Uganda, and Zambia comparing the prices of individually packaged ORS and zinc and the two products co-packaged. In all five countries, the co-packaged ORS and zinc product is less expensive—in most cases, significantly less expensive—than purchasing the two products separately.

Table 7. Illustrative prices of oral rehydration salts and zinc sold separately and in a co-pack.

				ORS and zinc			
Country	Retailer	ORS single 1 L sachet	Zinc dispersible tablet blister pack (10 tablets)	Purchased separately	Co-pack	Purchased separately (using October 2018 exchange rate)	Co-pack (using October 2018 exchange rate)
Ghana, 2018					2 GHC		US$0.41
Kenya, 2015	Pharmacies	10 KES	100 KES	120 KES	60 KES	US$1.28	US$0.59
Nigeria, 2016	Proprietary and patent medicine vendors	50 NGN	120 NGN	220 NGN	200 NGN	US$0.61	US$0.55
Uganda, 2015	Drug shops	500 UGX	2,000 UGX	3,000 UGX	2,500 UGX	US$0.80	US$0.66
Zambia, 2018	Community shops	3 ZMW	10 ZMW	16 ZMW	15 ZMW	US$1.39	US$1.30
Zambia, 2018	Supermarkets	NA	NA		7 ZMW		US$0.61

Sources: Kenya, Nigeria, and Uganda (Clinton Health Access Initiative Essential Medicines team); Ghana (Abt Associates' Sustaining Health Outcomes through the Private Sector Plus project team); Zambia (ColaLife).

12. Summary of regulatory status and market availability of the medicine

ORS is typically available in countries as an over-the-counter product and can be distributed without a physician prescription. While zinc previously had not been classified for sale over the counter in many countries, great progress was made as of 2015, when the Millennium Development Goals were supposed to have been met; zinc is now classified as an over-the-counter product in nine of the ten countries with the highest diarrheal disease burden: Bangladesh; the Democratic Republic of the Congo; India; Kenya; Niger; Nigeria; Pakistan; Tanzania; and Uganda (Annex VI).[Error! Bookmark not defined.0] Dr. Habtamu Seyoum, program manager for the Clinton Health Access Initiative Child Survival Program, reported in August 2018 that the tenth country, Ethiopia, achieved this classification in 2016.

13. Availability of pharmacopeial standards

ORS and zinc dosage forms have International Pharmacopoeia, United States Pharmacopeia, British Pharmacopeia, and Indian Pharmacopoeia standards.

Oral rehydration salts

- The International Pharmacopoeia, Seventh Edition, 2017,[63] oral rehydration salts
- The United States Pharmacopeia (USP 39)—National Formulary (NF 34),[64] oral rehydration salts
- The British Pharmacopoeia 2013,[65] oral rehydration salts
- The Indian Pharmacopoeia, 2010,[66] oral rehydration salts

Zinc

- The International Pharmacopoeia, Seventh Edition, 2017,[633] paediatric zinc sulfate oral solution
- The International Pharmacopoeia, Seventh Edition, 2017,[633] paediatric zinc sulfate tablets
- The United States Pharmacopeia (USP 39)—National Formulary (NF 34),[644] zinc sulfate oral solution
- The British Pharmacopoeia 2013,[655] zinc sulfate monohydrate capsules
- The British Pharmacopoeia 2013,[655] zinc sulfate monohydrate tablets

14. References

1. World Health Organization (WHO). *WHO Model List of Essential Medicines*. 20th List. Geneva: WHO; March 2017 (amended August 2017). http://www.who.int/medicines/publications/essentialmedicines/en/.

2. World Health Organization (WHO). *WHO Model List of Essential Medicines for Children*. 6th List. Geneva: WHO; March 2017 (amended August 2017):31. http://www.who.int/medicines/publications/essentialmedicines/en/.

3. World Health Organization (WHO), United Nations Children's Fund (UNICEF). *WHO/UNICEF Joint Statement: Clinical Management of Acute Diarrhoea*. New York NY, USA: UNICEF; 2004. http://www.who.int/maternal_child_adolescent/documents/who_fch_cah_04_7/en/.

4. Countdown to 2030 Collaboration. Countdown to 2030: tracking progress towards universal coverage for reproductive, maternal, newborn, and child health. *Lancet*. 2018;391(10129):1538–1548. https://doi.org/10.1016/S0140-6736(18)30104-1.

5. World Health Organization (WHO). *WHO Model Formulary for Children 2010*. Geneva: WHO; 2010. http://apps.who.int/iris/handle/10665/44309.

6. Munos MK, Walker CL, Black RE. The effect of oral rehydration solution and recommended home fluids on diarrhoea mortality. *International Journal of Epidemiology*. 2010;39(Suppl 1):i75–i87. doi:10.1093/ije/dyq025.

7. Walker CLF, Black RE. Zinc for the treatment of diarrhoea: effect on diarrhoea morbidity, mortality and incidence of future episodes. *International Journal of Epidemiology*. 2010;39(Suppl 1):i63–i69. doi:10.1093/ije/dyq023.

8. Bhutta ZA, Bird SM, Black RE, et al. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. *American Journal of Clinical Nutrition*. 2000;72(6):1516–1522. doi:10.1093/ajcn/72.6.1516.

9. Strand TA, Chandyo RK, Bahl R, et al. Effectiveness and efficacy of zinc for the treatment of acute diarrhea in young children. *Pediatrics*. 2002;109(5):898–903.

10. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. *Cochrane Database of Systematic Reviews*. 2012;(6):CD005436. doi:10.1002/14651858.CD005436.pub3.

11. International Vaccine Access Center, The Johns Hopkins University Bloomberg School of Public Health. *Pneumonia & Diarrhea Progress Report 2017: Driving Progress through Equitable Investment and Action*. Baltimore MD, USA: The Johns Hopkins University; 2017. https://www.jhsph.edu/ivac/wp-content/uploads/2018/04/IVAC-2017-Pneumonia-Diarrhea-Progress-Report-2.pdf.

12. Kar SS. Concept of essential medicines and rational use in public health. *Indian Journal of Community Medicine*. 2010;35(1):10–13. doi:10.4103/0970-0218.62546.

13. PATH, World Health Organization, United Nations Population Fund. *Essential Medicines for Reproductive Health: Guiding Principles for Their Inclusion on National Medicines Lists*.

Seattle WA, USA: PATH; 2006. http://www.who.int/medicines/publications/EssMeds_RHealth.pdf.

14. World Health Organization website. Essential medicines and health products: Essential medicines page. http://www.who.int/medicines/services/essmedicines_def/en/. Accessed August 28, 2018.

15. Mills A. Health care systems in low- and middle-income countries. *New England Journal of Medicine*. 2014;370:552–557. doi:10.1056/NEJMra1110897.

16. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1151–1210. doi:10.1016/S0140-6736(17)32152-9.

17. Fischer Walker CL, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet*. 2013;381(9875):1405–1416. https://doi.org/10.1016/S0140-6736(13)60222-6.

18. Fischer Walker CL, Perin J, Aryee MJ, Boschi-Pinto C, Black RE. Diarrhea incidence in low- and middle-income countries in 1990 and 2010: a systematic review. *BMC Public Health*. 2012;12:220. https://doi.org/10.1186/1471-2458-12-220.

19. GBD 2015 Diarrhoeal Diseases Collaborators. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infectious Diseases*. 2017;17(11):909–948. doi:10.1016/S1473-3099(17)30396-1.

20. World Health Organization/Control of Diarrhoeal Diseases (CDD). *Country Programme Profile for: Egypt*. World Health Organization; 1992.

21. Enzley S, Burros F. *A Global Review of Diarrhoeal Disease Control*. UNICEF Staff Working Papers, Evaluation, Policy and Planning Series, Number EVL-97-002. New York NY, USA: United Nations Children's Fund; 1997. https://www.unicef.org/evaldatabase/files/Global_1997_A_Global_Review.pdf.

22. National Control of Diarrheal Diseases Project 1998.

23. el-Rafie M, Hassouna WA, Hirschhorn N, et al. Effect of diarrhoeal disease control on infant and childhood mortality in Egypt. Report from the National Control of Diarrheal Diseases Project. *Lancet*. 1990;35(8685):334–338.

24. Cobb, LK, Baer, FC, Debay, MJP, et al. *Final Assessment of the Egypt Child Survival Project*. POPTECH Report, Number 96-073-41. Washington DC, USA: USAID Mission to Egypt; 1996.

25. Forsberg BC, Petzold MG, Tomson G, Allebeck P. Diarrhoea case management in low- and middle-income countries — an unfinished agenda. *Bulletin of the World Health Organization*. 2007;85(1):42–48.

26. Bhutta ZA, Das JK, Walker N, Rizvi A, Campbell H, Rudan I, Black RE; Lancet Diarrhoea and Pneumonia Interventions Study Group. Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? *Lancet*. 2013;381(9875):1417–1429. doi:10.1016/S0140-6736(13)60648-0.

27. Chopra M, Mason E, Borrazzo J, et al. Ending of preventable deaths from pneumonia and diarrhoea: an achievable goal. *Lancet*. 2013;381(9876):1499–1506. https://doi.org/10.1016/S0140-6736(13)60319-0.

28. Fischer Walker CL, Fontaine O, Young M, Black RE. Zinc and low osmolarity ORS for diarrhoea: a renewed call to action. *Bulletin of the World Health Organization*. 2009;87(10):780–786. doi:10.2471/BLT.08.058990.

29. Gill CJ, Young M, Shroder K, et al. Bottlenecks, barriers, and solutions: results from multi-country consultations focused on reduction of childhood pneumonia and diarrhoea deaths. *Lancet*. 2013;381(9876):1487–1498. https://doi.org/10.1016/S0140-6736(13)60314-1.

30. Werner D, Sanders D. *Questioning the Solution: The Politics of Primary Health Care and Child Survival*. Palo Alto CA, USA; HealthWrights; 1997.

31. Roche M, Meza RG, Vossenaar M. An intervention to co-package zinc and oral rehydration salts (ORS) improves health provider prescription and maternal adherence to WHO-recommended diarrhea treatment in western Guatemala. *The FASEB Journal*. 2015;29(1):902–912.

32. Gebremedhim S, Mamo G, Gezahign H, Kung'u J, Adish A. The effectiveness of bundling zinc with oral rehydration salts (ORS) for improving adherence to acute watery diarrhea treatment in Ethiopia: cluster randomised controlled trial. *BMC Public Health*. 2016;16:457. doi:10.1186/s12889-016-3126-6.

33. Ramchandani R. *Emulating Commercial, Private-Sector Value-Chains to Improve Access to ORS and Zinc in Rural Zambia: Evaluation of the Colalife Trial*. Dissertation submitted to The Johns Hopkins University in conformity with the requirements for the degree of Doctor of Public Health. 2016. https://jscholarship.library.jhu.edu/handle/1774.2/39229.

34. United Nations Children's Fund (UNICEF), World Health Organization (WHO). *Tracking Progress Towards Universal Coverage for Women's, Children's and Adolescents' Health: The 2017 Report*. Washington DC, USA: UNICEF and WHO; 2017. https://data.unicef.org/wp-content/uploads/2018/01/Countdown-2030.pdf.

35. Hill S, Yang A, Bero L. Priority medicines for maternal and child health: a global survey of national essential medicines lists. *PLOS ONE*. 2012;7(5):e38055. https://doi.org/10.1371/journal.pone.0038055.

36. Reproductive Health Supplies Coalition website. EML Search: Database of Family Planning and Maternal Health Commodities in National Essential Medicines Lists page. http://www.cecinfo.org/EMLSearch/. Accessed August 24, 2018.

37. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS; The Bellagio Child Survival Study Group. How many child deaths can we prevent this year? *Lancet*. 2000;362(9377):65–71. https://doi.org/10.1016/S0140-6736(03)13811-1.

38. World Health Organization (WHO). *Reduced Osmolarity: Oral Rehydration Salts (ORS) Formulation. A Report from a Meeting of Experts Jointly Organised by UNICEF and WHO: UNICEF house, New York, USA, 18 July 2001*. Geneva: WHO; 2002. http://apps.who.int/iris/handle/10665/67322.

39. Fischer Walker CL, Black RE. Zinc for the treatment of diarrhoea: effect on diarrhoea morbidity, mortality and incidence of future episodes. *International Journal of Epidemiology*. 2010;39(Suppl 1):i63–i69. doi:10.1093/ije/dyq023.

40. Goh N, Pollak K. *Progress over a Decade of Zinc and ORS Scale-up: Best Practices and Lessons Learned*. Boston MA, USA: Clinton Health Access Initiative; 2016. https://clintonhealthaccess.org/content/uploads/2016/02/Progress-over-a-Decade-of-Zinc-and-ORS-Scale-Up.pdf.

41.Lam F. Barriers and Opportunities in Driving Down the Burden of Diarrheal Disease Among Children Under Age 5: Where Do We Go from Here? Going to scale: Lessons learned from programs in India, Kenya, Nigeria, and Uganda [panel symposium presentation]. American Society of Tropical Medicine & Hygiene 67th Annual Meeting, November 1, 2018; New Orleans LA, USA.

42. Lenters LM, Das JK, Bhutta ZA. Systematic review of strategies to increase use of oral rehydration solution at the household level. *BMC Public Health*. 2013;13(Suppl 3):S28. https://doi.org/10.1186/1471-2458-13-S3-S28.

43. Borapich D, Warsh M. Improving child health in Cambodia: social marketing of diarrhea treatment kit, results of a pilot project. *Cases in Public Health Communication & Marketing*. 2010;4:4–22.

44. Habib MA, Soofi S, Sadik K, et al. A study to evaluate the acceptability, feasibility and impact of packaged interventions ("Diarrhea Pack") for prevention and treatment of childhood diarrhea in rural Pakistan. *BMC Public Health*. 2013;13:922. doi:10.1186/1471-2458-13-922.

45. World Health Organization (WHO), United Nations Children's Fund. *Diarrhoea: Why Children Are Still Dying and What Can be Done*. Geneva: WHO; 2009. http://www.who.int/maternal_child_adolescent/documents/9789241598415/en/.

46. World Health Organization (WHO). *Implementing the New Recommendations on the Clinical Management of Diarrhoea: Guidelines for Policy Makers and Programme Managers*. Geneva: WHO; 2006. http://apps.who.int/iris/bitstream/handle/10665/43456/9241594217_eng.pdf;jsessionid=14F469162BB3460B8D639F9BE276AB24?sequence=1.

47. United Nations Children's Fund (UNICEF) Supply Division. *Oral Rehydration Salts and Zinc: UNICEF Suppliers and Product Range*. København, Denmark: UNICEF; 2016. https://www.unicef.org/supply/files/ORS_and_Zinc_Supply_Update.pdf.

48. Water with sugar and salt [editorial]. *Lancet*. 1978;312(8084):300–301. https://doi.org/10.1016/S0140-6736(78)91698-7.

49. World Health Organization (WHO). *WHO Drug Information*. Volume 16, Number 2. Geneva: WHO; 2002. http://apps.who.int/medicinedocs/en/d/Js4950e/.

50. Moritz ML. Fluid replacement for severe hyponatremia. *Journal of the American Medical Association*. 2006;296(5):567–573. Doi:10.1001/jama.297.1.41-a.

51. World Health Organization (WHO). *The Treatment of Diarrhoea: A Manual for Physicians and Other Senior Health Workers*. Geneva: WHO; 2005. http://www.who.int/maternal_child_adolescent/documents/9241593180/en/.

52. Bajaita C, Thawani V. Role of zinc in pediatric diarrhea. *Indian Journal of Pharmacology*. 2011;43(3):232–235. doi:10.4103/0253-7613.81495.

53. United Nations Children's Fund (UNICEF), World Health Organization (WHO). *Evidence for the Safety and Efficacy of Zinc Supplementation in the Management of Diarrhoea*. New York NY, USA: UNICEF and WHO; 2007. http://www.zinctaskforce.org/wp-content/uploads/2011/06/WHO-UNICEF-2007_Evidence-for-the-Safety-and-Efficacy-of-Zinc-Supplementation-in-the-Management-of-Diarrhoea.pdf.

54. Lukacik M, Thomas RL, Aranda JV. A meta-analysis of the effects of oral zinc in the treatment of acute and persistent diarrhea. *Pediatrics*. 2008;121(2):326–336. doi:10.1542/peds.2007-0921.

55. Sazawal S, Malik P, Jalla S, Krebs N, Bhan MK, Black RE. Zinc supplementation for four months does not affect plasma copper concentration in infants. *Acta Paediatrica*. 2004;93(5):599–602.

56. Bhatnagar S, Bahl R, Sharma PK, Kumar GT, Saxena SK, Bhan MK. Zinc with oral rehydration therapy reduces stool output and duration of diarrhoea in hospitalized children: a randomized controlled trial. *Journal of Pediatric Gastroenterology and Nutrition*. 2004;38(1):34–40.

57. Bhutta ZA, Nizami SQ, Isani Z. Zinc supplementation in malnourished children with persistent diarrhoea in Pakistan. *Pediatrics*. 1999;103(4):e42.

58. Léonard A, Gerber GB, Léonard F. Mutagenicity, carcinogenicity and teratogenicity of zinc. *Mutation Research*. 1986;168(3):343–353.

59. World Health Organization (WHO). *Priority Medicines for Mothers and Children 2011*. Geneva: WHO; 2011. http://apps.who.int/medicinedocs/documents/s17992en/s17992en.pdf.

60. Gregorio GV, Gonzales MLM, Dans LF, Martinez EG. Polymer-based oral rehydration solution for treating acute watery diarrhoea. *Cochrane Database of Systematic Reviews*. 2009;15(2):CD006519. doi:10.1002/14651858.CD006519.pub2.

61. Baqui AH, Black RE, El Arifeen S, et al. Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. *BMJ*. 2002;325(7372):1059. doi:10.1136/bmj.325.7372.1059.

62. Lamberti LM, Walker CLF, Taneja S, Mazumder S, Black RE. Adherence to zinc supplementation guidelines for the treatment of diarrhea among children under–five in Uttar Pradesh, India. *Journal of Global Health*. 2015;5(2):020410. doi:10.7189/jogh.05.020410.

63. World Health Organization (WHO). *The International Pharmacopoeia*. 7th ed. Geneva: WHO; 2017. http://apps.who.int/phint/en/p/about/.

64. USP-NF [United States Pharmacopeia National Formulary] website. USP 39–NF 34 page. https://www.uspnf.com/official-text/proposal-statuscommentary/usp-39-nf-34. Accessed August 30, 2018.

65. United Kingdom Medicines & Healthcare products Regulatory Agency (MHRA). *British Pharmacopoeia 2013*. London: MHRA; 2012.

66. Indian Pharmacopoeia Commission. *Indian Pharmacopoeia 2010*. 6th ed. 2009.

Annex I. Concept note: Co-packaged oral rehydration salts and zinc – next phase

From global policy to national adoption and scale-up

The overall goal of the next phase of this project would be twofold: (1) support country-driven development of policy and guidelines toward ORS and zinc introduction and scale as part of essential newborn and child health programs and/or procurement lists; and (2) ensure that the new global guidance around co-packaged ORS and zinc is widely shared and understood among key global and national audiences (policymakers, advocates, decision-makers). We envision that within 5 to 7 years of inclusion on the WHO EMLc, a significant number of countries with the highest diarrheal disease prevalence will have included co-packaged ORS and zinc on their national essential medicines list (NEML) and are either introducing or scaling co-packaged ORS and zinc, or are planning to introduce in the near future.

Below is a list of four main categories of activities we are currently discussing to help achieve our overall goal. We intend to continue refining this plan in the next few months with input from partners, stakeholders, and funders.

1. **Ensure stakeholder coordination and alignment**
    - Leverage ongoing in-country policy initiatives and other national policy work. For example, PATH's ongoing work to incorporate lifesaving maternal, newborn, and child health (MNCH) and enteric and diarrheal disease/pneumonia commodities (including ORS and zinc) into targeted national MNCH policies and plans in the Democratic Republic of the Congo, Kenya, and Uganda; Abt Associates' Sustaining Health Outcomes through the Private Sector Plus initiative; and the Clinton Health Access Initiative's work in priority countries could serve as important platforms. We will conduct a landscape to audit key opportunities and use the findings to further help with country categorization and prioritization of policy work.
2. **Support in-country decision-making for policy and strategy development**
    - Support country-driven development of policy and guidelines toward co-packaged ORS and zinc introduction and scale-up. This work stream would need to be customized by country/region based on what type of support is needed. A range of activities could include participation in key relevant technical working groups and subnational management committees; specific policy development support and dissemination workshops; joining relevant planning processes at national and subnational levels; one-on-one meetings with key decision-makers; and organizing policy dialogues to strengthen engagement and coordination for policy planning and implementation and resource allocation.
3. **Increase issue salience and political will**
    - Develop and disseminate global communication assets to help raise awareness of the new normative guidance around co-packaged ORS and zinc among priority audiences (e.g., a

suite of evidence-based materials including a project brief, technical infographics, an op-ed, a case study, a video).

- Support local communications strategies to amplify their advocacy efforts (e.g., engaging local media, working with local civil society partners to build targeted national engagement digital strategies, developing/adopting global content to appeal to national and subnational audiences, incorporating local asks for policy change).

4. Enable knowledge and resource management

- Develop a knowledge management mechanism to share information between the global and country levels, and to allow countries to leverage their experience and knowledge to accelerate introduction (e.g., regional workshops, learning exchanges/meet-ups, regional learning labs, showcasing country perspectives at key global and regional forums). Drawing on the experiences of countries in which a co-packaged product has already been added to the NEML, these exchanges will support decision-makers to identify common technical and tactical problems, model solutions, and share results.
- Develop and disseminate tools and guidance documents (e.g., technical brief summarizing evidence and availability of co-packaged ORS and zinc, guidance documents for national policy and program development, case studies) to facilitate knowledge-sharing.
- With regard to uptake at the country level, track and research the impact of including co-packaged ORS and zinc on the WHO EMLc.

Annex II. Consultation meeting on increasing access to oral rehydration salts and zinc sulfate through normative policy change

Monday, June 25, 2018 | 2:00–4:00 pm Central European Time | PATH Geneva office

A consultation meeting was held at the PATH office in Geneva, Switzerland, to consider the first draft of this application to include co-packaged oral rehydration salts (ORS) and zinc sulfate (zinc) on the WHO Model List of Essential Medicines for Children (EMLc).

Participants

Per Ashorn, Department of Maternal, Newborn, Child and Adolescent Health (MCA), WHO
Simon Berry, ColaLife
Philippe Guinot, PATH
Lorenzo Moja, Model List of Essential Medicines (EML), WHO
Rohit Ramchandani, Antara Global Health Advisors and ColaLife (via Skype)
Jonathon Simon, MCA, WHO

Discussion highlights

1. Overall consensus is that there had been a great start to the application, and that WHO (EML Secretariat and MCA unit) are looking forward to seeing the next draft in early September 2018.
2. The Diarrhea Innovations Group (DIG) indicated they saw this application and the listing of co-packaged ORS and zinc on the WHO EMLc as the precursor to increasing coverage of ORS and zinc for the treatment of diarrhea. The WHO EML influences national essential medicines lists (NEMLs), which in turn influence national health policies, budgets, and donor support.
3. WHO commented that this wider objective would be assisted if the application were considered under the EML Expert Committee's "main agenda" rather than the "consent agenda." Although the "consent agenda" is the path of least resistance to an EML listing, there is less formal discussion and recommendation from the EML Secretariat/Expert Committee. So there would be an advantage if this application were considered under the main agenda with regard to the implementation/adoption work that will inevitably need to follow to achieve the broader DIG objective of increased coverage. It is WHO that decides under which agenda the application is considered.
4. DIG should include information on the plans, after co-packaged ORS/zinc is listed, with regard to implementation/adoption/demand generation (e.g., advocacy efforts, recommendations for caregivers, dissemination for population-level targeting, Wikipedia

instructions/guidance, action targeting policymakers). This would improve our chances of getting our application on the main agenda.

5. Information from Olivier Fontaine (key historical perspective) noted that a previous attempt to list co-packaged ORS and zinc was not accepted because of restrictions at country level on sales of co-packaged pharmaceuticals. However, this is no longer seen as an issue from WHO's perspective. Although it is noted that there may still be some resistance in some individual countries.
6. It was recommended that DIG pursue its plans to get the United Nations Children's Fund (UNICEF) involved in the application.
7. The application needs to be very clear that it is making the case for the listing of co-packaged ORS and zinc in addition to having ORS and zinc listed separately (as they are now).
8. Key message narrative:
    - ORS and zinc are highly effective against childhood diarrhea.
    - Zinc use is much too low.
    - Evidence shows that co-packaging can reverse this.
    - An EML listing and follow-up work will help advance coverage of the combined use of ORS and zinc for the treatment of diarrhea.
9. WHO recommended the inclusion of photographs (e.g., of co-packaged products already available) and case studies.
10. WHO made the point that we are not facing a scientific or technical issue, we are facing a demand issue. To address this, we need to use the EML as a catalyst, UNICEF as a major procurer, and NEMLs to spur country-level adoption. We have failed at zinc thus far; the conditional probability of having both ORS and zinc in stock at the same time is low (e.g., some facilities have not seen zinc in two years)—but we have examples of how demand can be transformed through co-packaging.
11. May be worth discussing: sachet sizes; home treatment versus facility treatment versus nutritional requirements; hydration levels required.
12. The application would be endorsed by WHO (MCA) rather than being a WHO/DIG co-application. WHO MCA is happy to endorse and will review and provide input to a near final draft in September 2018.
13. WHO MCA will help us develop a narrative around linkage to WHO's newly approved General Programme of Work.
14. From a research perspective, there is interest from journals in the process of getting an idea like co-packaging adopted into national policies and the impact with regard to uptake of ORS/zinc globally as a result of an EML listing.

Annex III. Letters of support

Abt Associates, Catherine Clarence, Child Health Advisor, SHOPS Plus, International Development Division, Washington, DC, United States

Aga Khan University, Dr. Zulfiqar A. Bhutta, Professor and Founding Director, Center of Excellence in Women & Child Health, Karachi, Pakistan

Bill & Melinda Gates Foundation, Dr. Anita Zaidi, Director, Enteric & Diarrheal Disease, Global Health, Seattle, WA, United States

Clinton Health Access Initiative, Kate Schroder, Vice President, Essential Medicine Initiative, Boston, MA, United States

Ghana Health Services, Mr. Leonard Lamptey, Convenor, Working Group for Essential Health Commodities, Accra, Ghana

Institute for Health Metrics and Evaluation, Dr. Chris Murray, Institute Director, Chair and Professor, Department of Health Metrics Sciences, University of Washington, Seattle, WA, United States

Johns Hopkins Bloomberg School of Public Health, Dr. David Sack, Professor, Department of International Health, Baltimore, MD, United States

Pharmanova Zambia, Ltd., Mr. Mohammed Umar, Director, Lusaka, Zambia

Senegal Ministry of Health and Social Welfare, Dr. Omar Sarr, [need title], Dakar, Senegal

United Nations Children's Fund, Dr. Rory Nefdt, Chief, Child and Community Health, New York, NY, United States

In addition to the letters included here, an email expressing support was sent by the United States Agency for International Development directly to emlsecretariat@who.int.

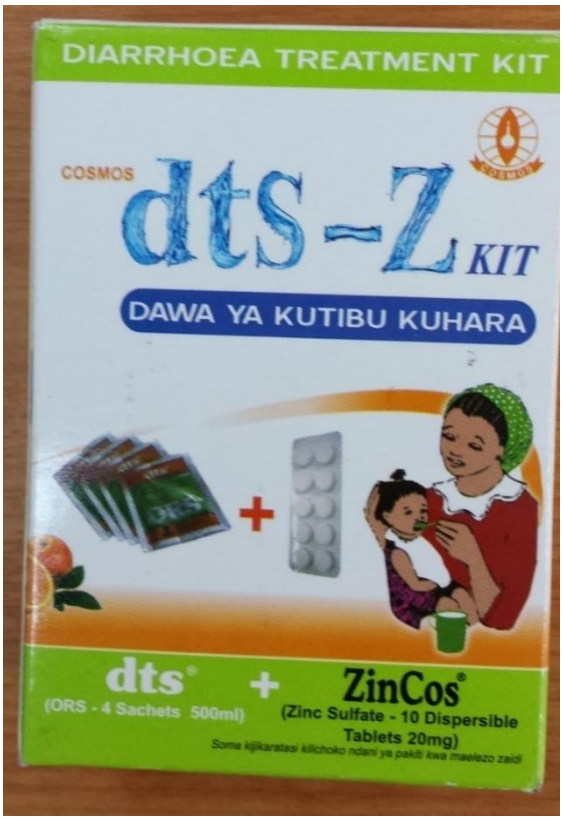
Annex IV. World Health Organization normative guidance on the clinical use of oral rehydration salts and zinc sulfate

Year	Title	Resource link
2013	Ending Preventable Child Deaths from Pneumonia and Diarrhoea by 2025: The Integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD)	http://www.who.int/maternal_child_adolescent/documents/global_action_plan_pneumonia_diarrhoea/en/
2011	Caring for Newborns and Children in the Community: Caring for the sick child in the community	http://www.who.int/maternal_child_adolescent/documents/imci_community_care/en/
2011	Priority medicines for mothers and children 2011: Ensuring access to priority medicines for mothers and children improves health and saves lives	http://www.who.int/maternal_child_adolescent/documents/emp_mar2011.1/en/
2010	Facts for Life (fourth edition)	http://www.who.int/maternal_child_adolescent/documents/9789280644661/en/
2010	WHO recommendations on the management of diarrhoea and pneumonia in HIV-infected infants and children	http://www.who.int/maternal_child_adolescent/documents/9789241548083/en/
2009	Diarrhoea: Why children are still dying and what can be done	http://www.who.int/maternal_child_adolescent/documents/9789241598415/en/
2009	Identifying priorities for child health research to achieve Millennium Development Goal 4: Consultation Proceedings, Geneva, 26–27 March 2009	http://www.who.int/maternal_child_adolescent/documents/9789241598651/en/
2008	Introducing Zinc in a Diarrhoeal Disease Control Programme: Guide to conducting formative research	http://www.who.int/maternal_child_adolescent/documents/9789241596473/en/
2007	Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers	http://www.who.int/maternal_child_adolescent/documents/9241594942/en/
2006	Implementing the New Recommendations on the Clinical Management of Diarrhoea: Guidelines for Policy Makers and Programme Managers	http://www.who.int/maternal_child_adolescent/documents/9241594217/en/
2006	Oral rehydration salts: Production of the new ORS	http://www.who.int/maternal_child_adolescent/documents/fch_cah_06_1/en/
2005	The treatment of diarrhoea: A manual for physicians and other senior health workers	http://www.who.int/maternal_child_adolescent/documents/9241593180/en/

Year	Title	Resource link
2004	WHO/UNICEF joint statement: Clinical management of acute diarrhea	http://www.who.int/maternal_child_adolescent/documents/who_fch_cah_04_7/en/
2004	Diarrhoea Treatment Guidelines including new recommendations for the use of ORS and zinc supplementation for Clinic-Based Healthcare Workers	https://hetv.org/pdf/diarrhoea-guidelines.pdf

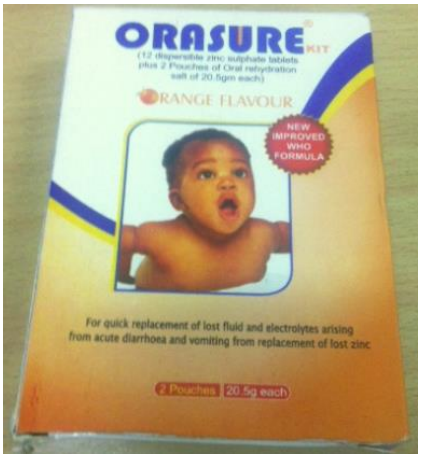
Annex V. Examples of current applications of oral rehydration salts and zinc sulfate co-packs in Kenya, Nigeria, and Uganda

Kenya



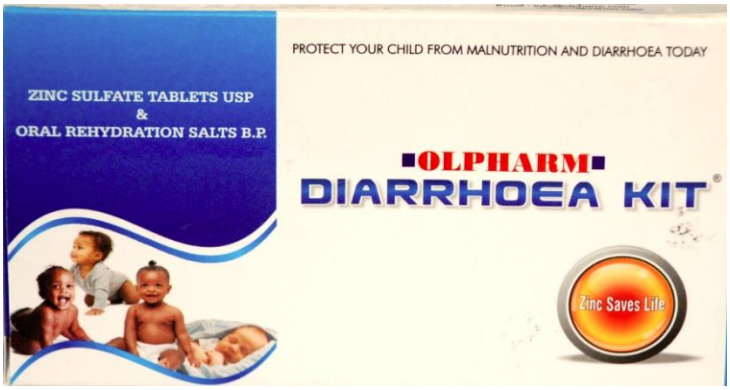
dts-Z Kit, universal co-pack for diarrhea treatment, Orazinc Kit. Photos: Clinton Health Access Initiative.

Nigeria



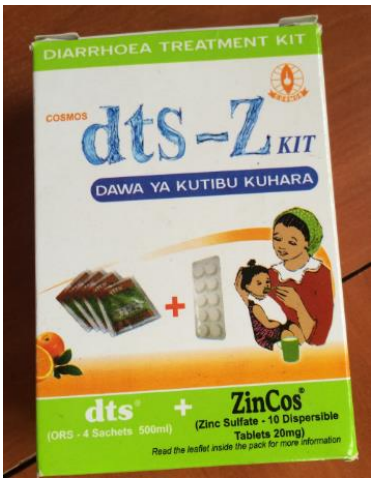
EmzolytePlus, Fidson, Diarrhea Treatment Kit, Orasure. Photos: Clinton Health Access Initiative.

Nigeria (cont.)



Motitec co-pack, CHI co-pack, Olpharm. Photos: Clinton Health Access Initiative.

Uganda



dts-Z Kit, Oralyte Co-Pack, RestORS + ZinKid co-pack, ZinkOra Kit, D-Lyte Co-Pack. Photos: Clinton Health Access Initiative.

Zambia

Kit Yamoyo anti-diarrhoea kit: Kit Yamoyo Screw-top, Kit Yamoyo Flexi-pack, and government-branded Flexi-pack. Photos: ColaLife.

Annex VI. Relationship to the Sustainable Development Goals

In the lead-up to the 2015 deadline for meeting the Millennium Development Goals, the Diarrhea and Pneumonia Working Group, coordinated by the Clinton Health Access Initiative, led a concerted effort in each of the ten countries[d] with the highest diarrheal disease burden to make progress toward reducing diarrheal deaths. The group identified four factors that contribute to large-scale and sustained increases in coverage of oral rehydration salts (ORS) and zinc sulfate (zinc), and, in turn, to improved diarrheal disease treatment:

1. Facilitating a strong enabling environment.
2. Improving availability of high-quality and affordable supply.
3. Improving knowledge and skills of health providers.
4. Generating demand among caregivers.

Progress over a Decade of Zinc and ORS Scale-up: Best Practices and Lessons Learned,[e] produced in February 2016, highlighted progress on these four factors. For example, from 2005 to 2015 nine of the ten high-burden countries (all but Ethiopia) achieved over-the-counter status for zinc. Ethiopia has since reached this status.

While significant progress has been made in ORS and zinc coverage, in large part as a result of improvements on all four factors, significant disparities remain. As of 2016, in 13 countries with available data (of the 15 with the highest mortality from childhood pneumonia and diarrhea), ORS treatment ranged from 20% (Chad and Sudan) to 77% (Bangladesh). Zinc supplementation, among children with diarrhea, in the 11 countries with available data of the 15 high-burden countries, was much lower, ranging from 0% (Ethiopia, India, and Somalia) to 49% (Bangladesh).[f] It is anticipated that co-packaged ORS and zinc will contribute to improved coverage of both ORS and zinc and increase access. The latest Countdown to 2030 report found 43 countries with data on the use of ORS and zinc for childhood diarrhea, with coverage ranging from 0% (Dominican Republic, The Gambia, and Tajikistan) to 60% (Bolivia).[g]

The proposed work sets out to help advance global progress toward Sustainable Development Goal 3 by promoting wider use of co-packaged ORS and zinc as an integral part of the global

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d. Bangladesh, Democratic Republic of the Congo, Ethiopia, India, Kenya, Niger, Nigeria, Pakistan, Tanzania, and Uganda.

e. Goh N, Pollak K. *Progress over a Decade of Zinc and ORS Scale-up: Best Practices and Lessons Learned*. Boston MA, USA: Clinton Health Access Initiative; 2016. https://clintonhealthaccess.org/content/uploads/2016/02/Progress-over-a-Decade-of-Zinc-and-ORS-Scale-Up.pdf.

f. International Vaccine Access Center, The Johns Hopkins University Bloomberg School of Public Health. *Pneumonia & Diarrhea Progress Report 2017: Driving Progress through Equitable Investment and Action*. Baltimore MD, USA: The Johns Hopkins University; 2017. https://www.jhsph.edu/ivac/wp-content/uploads/2018/04/IVAC-2017-Pneumonia-Diarrhea-Progress-Report-2.pdf.

g. United Nations Children's Fund (UNICEF), World Health Organization (WHO). *Tracking Progress Towards Universal Coverage for Women's, Children's and Adolescents' Health: The 2017 Report*. Washington DC, USA: UNICEF and WHO; 2017. https://data.unicef.org/wp-content/uploads/2018/01/Countdown-2030.pdf.

solution to diarrheal disease—a leading cause of child mortality. This work has the potential to positively improve the lives of millions of children—especially young children living in low- and middle-income countries where the burden of diarrhea is the greatest—and protect them from death and disability. Long-term benefits to families and communities (as a result, in part, of cost savings to households from home treatment with ORS and zinc versus hospitalization) also help advance progress toward other Sustainable Development Goals (e.g., 1, 2, 4, and 8) by increasing wellness, productivity, and social and economic activity, along with reducing total long-term health care costs to families, communities, and countries.