

# SCALING UP ORAL REHYDRATION SOLUTION AND ZINC CO-PACKS FOR THE TREATMENT OF DIARRHEA IN UNDER-5-YEAR-OLDS

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**APRIL 2023**

**RECOMMENDED**

# Research Report:

## Large-Scale Global Health – Scaling up Oral Rehydration Solution and zinc co-packs for the treatment of diarrhea in under-5-year-olds

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**Date of publication:**

**Research period:** 2022

Thanks to Kylie Abel and Urszula Zarosa for their contributions to this report. We are also grateful to the experts who took the time to offer their thoughts on this research.

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## Executive summary

**Diarrhea is a common occurrence for children in rich and poor countries alike. Regrettably, under-five-year-olds continue to die extremely preventable deaths in many low-resource countries due to diarrhea, as they lack access to life-saving and cheap treatment.**

**Diarrheal diseases are the third leading cause of death in children under five in the world, with over 500,000 young lives taken in 2019.** Oral Rehydration Solution (ORS)<sup>1</sup> and zinc supplementation can avert most of these deaths, and has been known to help for decades.

There is **strong evidence that treatment of diarrhea with ORS reduces mortality.** A meta-analysis of 157 studies estimates that **ORS might prevent 93% of diarrhea deaths at full coverage.** A Cochrane review of 17 trials finds no clinically significant differences in outcomes when comparing oral vs intravenous rehydration. A systematic review of 13 RCTs suggests that (compared to ORS alone) **zinc can shorten the duration of prolonged diarrhea by a third,** and may prevent future diarrhoeal episodes in the two–three months following supplementation.

**We propose that a nonprofit organization can help scale treatment rates of diarrhea by delivering co-packaged ORS and Zinc to caregivers for free, before they have a need for it.**

Randomized controlled trials of door-to-door distribution of ORS show that this is a feasible intervention – one of these RCTs found that, compared to the control (where CHWs sell subsidized ORS and zinc), **delivering ORS and zinc for free to caregivers increased ORS treatment by 20 percentage points, and ORS+zinc treatment by 33 percentage points.**

This intervention also looks **cost-effective**, with an average cost-effectiveness of **~USD 188 per disability-adjusted life year (DALY)** averted in high-burden countries in our main model. It looks **particularly cost-effective in Chad, with an estimated cost-effectiveness of USD 57 per DALY averted,** and in **Yobe, Nigeria, at around USD 47 per DALY.**

We found that this intervention should be relatively **simple to run and deliver, talent should be easy to find,** and that **work in this space is neglected,** so there is space for a new charity.

However, there are also some important concerns. Experts have noted that **funding ORS and zinc interventions can be challenging,** as funders prefer prevention or

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<sup>1</sup> ORS is a mixture of water, sugar, and salt that treats dehydration.

other areas of global health, such as maternal and neonatal mortality. **The proportion of children reached with this intervention, that would have had risky cases of diarrhea, is unknown.** There are also **significant uncertainties about the real mortality effect of increases in ORS at scale.** These considerations could diminish the overall impacts of this intervention.

Overall, our view is that a new charity scaling up the distribution of ORS and zinc co-packs for the treatment of diarrhea in under 5-year-olds is an idea worth recommending to future charity founders.

# Table of contents

<a href="#"><u>Executive summary</u></a>	<a href="#"><u>2</u></a>
<a href="#"><u>Table of contents</u></a>	<a href="#"><u>4</u></a>
<a href="#"><u>Introduction</u></a>	<a href="#"><u>5</u></a>
<a href="#"><u>Background</u></a>	<a href="#"><u>6</u></a>
<a href="#"><u>The burden of diarrheal disease</u></a>	<a href="#"><u>6</u></a>
<a href="#"><u>Interventions to reduce diarrheal mortality</u></a>	<a href="#"><u>6</u></a>
<a href="#"><u>Theories of change</u></a>	<a href="#"><u>8</u></a>
<a href="#"><u>Geographic assessment</u></a>	<a href="#"><u>11</u></a>
<a href="#"><u>Where existing organizations work and the status of ORS and zinc in high-burden countries</u></a>	<a href="#"><u>11</u></a>
<a href="#"><u>Geographic Assessment</u></a>	<a href="#"><u>13</u></a>
<a href="#"><u>Burden</u></a>	<a href="#"><u>13</u></a>
<a href="#"><u>Tractability</u></a>	<a href="#"><u>13</u></a>
<a href="#"><u>Neglectedness</u></a>	<a href="#"><u>13</u></a>
<a href="#"><u>A note on the assessment</u></a>	<a href="#"><u>14</u></a>
<a href="#"><u>Quality of evidence</u></a>	<a href="#"><u>15</u></a>
<a href="#"><u>Evidence that a charity can make a change in this space</u></a>	<a href="#"><u>15</u></a>
<a href="#"><u>Free preemptive delivery by Community Health Workers</u></a>	<a href="#"><u>15</u></a>
<a href="#"><u>Co-promotion of ORS and zinc</u></a>	<a href="#"><u>16</u></a>
<a href="#"><u>Demand-generation ORS and zinc</u></a>	<a href="#"><u>17</u></a>
<a href="#"><u>Evidence that the change has the expected health effects</u></a>	<a href="#"><u>18</u></a>
<a href="#"><u>Expert views</u></a>	<a href="#"><u>19</u></a>
<a href="#"><u>Cost-effectiveness analysis</u></a>	<a href="#"><u>20</u></a>
<a href="#"><u>Effects</u></a>	<a href="#"><u>22</u></a>
<a href="#"><u>Costs</u></a>	<a href="#"><u>23</u></a>
<a href="#"><u>Alternative models</u></a>	<a href="#"><u>23</u></a>
<a href="#"><u>Model 2 - Yobe, Nigeria</u></a>	<a href="#"><u>23</u></a>
<a href="#"><u>Model 3 - lower costs and morbidity adjustments</u></a>	<a href="#"><u>23</u></a>
<a href="#"><u>Illustrative LiST projections</u></a>	<a href="#"><u>24</u></a>
<a href="#"><u>Implementation</u></a>	<a href="#"><u>25</u></a>
<a href="#"><u>Talent</u></a>	<a href="#"><u>25</u></a>
<a href="#"><u>Access</u></a>	<a href="#"><u>25</u></a>
<a href="#"><u>Information</u></a>	<a href="#"><u>25</u></a>
<a href="#"><u>Relevant stakeholders</u></a>	<a href="#"><u>25</u></a>
<a href="#"><u>Feedback loops</u></a>	<a href="#"><u>25</u></a>

<u>Funding</u>	<u>26</u>
<u>Effective Altruism organizations' funding</u>	<u>26</u>
<u>Funding in Global Health</u>	<u>26</u>
<u>Scale of the problem</u>	<u>26</u>
<u>Neglectedness</u>	<u>26</u>
<u>Tractability</u>	<u>27</u>
<u>Externalities</u>	<u>27</u>
<u>Remaining uncertainties</u>	<u>27</u>
<u>Conclusion</u>	<u>28</u>
<u>References</u>	<u>28</u>

## Introduction

This report has been produced by Charity Entrepreneurship (CE). CE's mission is to cause more effective charities to exist worldwide by connecting talented individuals with high-impact intervention opportunities. We achieve this goal through an extensive research process and our incubation program. In 2022, our research process focused on the top highly scalable global health interventions.

*Scaling up Oral Rehydration Solution (ORS) and zinc co-packs for the treatment of diarrhea in under-5-year-olds* was chosen by CE research staff as a potentially promising intervention within this category. This decision resulted from a five-month process to identify interventions that were most likely high-impact avenues for future charity entrepreneurs. This process began by listing nearly 300 ideas and gradually narrowing them down, examining them in more and more depth.

We use various decision-making tools such as group consensus decision-making, weighted-factor models, cost-effectiveness analyses, quality of evidence assessments, case-study analyses, and expert interviews, to assess how promising interventions would be for future charity entrepreneurs.

This process was exploratory and rigorous, but not comprehensive – we did not research all 300 ideas in depth. As such, our decision not to take forward a charity idea to the point of writing a full report should not be seen as a view that the idea is not good.

## Background

### The burden of diarrheal disease

**Diarrheal diseases are the third leading cause of death in children under five** ([Global Burden of Disease Collaborative Network, 2019](#)). **Almost 60% of deaths in under-fives occur in the top ten countries ordered by the number of deaths:** India, Nigeria, Pakistan, Ethiopia, the Democratic Republic of Congo (DRC), China, Niger, Tanzania, Mali, and Indonesia ([Global Burden of Disease Collaborative Network, 2019](#)).

The incidence of diarrheal diseases, particularly for infants, has not improved significantly in the last 40 years. This suggests that most of the 89% decrease in deaths between 1980 and 2015 occurred due to improved illness management ([Keusch et al., 2016](#)). Efficient treatment for diarrhea exists, but children worldwide fail to get it every day.

**Diarrhea is a common disease that, if managed correctly, is not lethal; in fact, the risk of dying of diarrhea is extremely low. In the richest European and Asian countries, the death rate due to diarrhea is as low as one death per 100,000 per year. In Madagascar, Chad, and the Central African Republic, the rate is 300 deaths per 100,000 per year.** The major risk factors for diarrhea in under-fives are lack of access to safe drinking water, poor sanitation, and malnutrition ([Dadonaite, Ritchie, & Roser, 2018](#)). These are much more prevalent in the poorest countries.

### Interventions to reduce diarrheal mortality

**Interventions in this work area can be broadly split into prevention and treatment.** Preventative interventions include vaccination (e.g., for rotavirus), clean water and sanitation, and improved nutrition. Treatment interventions include ORS, zinc supplementation, and antimicrobials for bloody diarrhea or dysentery ([Keusch et al., 2016](#); [Bhutta et al., 2013](#)).

ORS is a simple mixture of water, sugar, and salt that helps treat dehydration.<sup>2</sup> It was discovered as a workaround for a lack of supplies to treat diarrhea through

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<sup>2</sup> “The therapy works because the co-absorption of glucose and sodium is preserved during watery diarrheas; hence, ORS containing optimal concentrations of glucose and salt results in net uptake of sodium and chloride, effectively expanding the intravascular compartment regardless of age, and significantly reduces the need for intravenous fluids for all but the most severely dehydrated patients or those with intractable vomiting. New formulations with lower concentrations of glucose and sodium reduce the likelihood of hypernatremia during treatment of noncholera dehydration, reduce total stool output and vomiting, and reduce the need for supplementary intra-venous fluids (Hahn, Kim, and Garner 2002); the World Health Organization (WHO) now recommends such formulations (WHO and UNICEF 2004).” ([Keusch, et al., 2016, p.169](#))

intravenous rehydration.<sup>3</sup> Since then, it has been the poster child for simple and cheap solutions to big problems; the [Lancet \(1987\)](#) has called it “potentially the most important medical advance this century” (p.300). In 2007, researchers estimated that ORS had prevented over 50 million deaths ([Nalin & Cash, 2018](#)).

**The first study demonstrating the effectiveness of oral rehydration therapy in reducing diarrheal mortality was published over 50 years ago.** Since then, ORS has been one of the primary reasons for the decline in diarrheal mortality over recent decades ([Khan, Wright & Bhutta, 2020](#)). A systematic review suggests that ORS may prevent death due to diarrhea in 93% of cases at 100% coverage ([Munos, Fischer Walker, & Black, 2010](#)).

**Despite its status, ORS coverage rates have stalled at around an average of 40% of diarrhea cases treated** ([Khan, Wright & Bhutta, 2020](#); [Dadonaite, Ritchie, & Roser, 2018](#)). In some high-burden countries, treatment with ORS can be as low as 13.6% ([World Bank, 2023](#)).

Barriers to uptake seem to be quite context-dependent. Still, they include

- **Availability:** Several papers have noted that the lack of readily available ORS acted as a barrier to uptake in ORS interventions across Bangladesh, Nigeria, Egypt, and India ([Ezezika et al., 2021](#)). ORS and zinc production is not very profitable, and local producers may be unable to cushion upfront costs to set up cheap and sustainable supply chains ([Berry Interview](#)).
- **Caregiver behavior:** Some studies and experts suggest that caregiver understanding of ORS as a proper treatment is low ([Keusch et al., 2016](#)). Caregivers may perceive it as a “non-medical” and inefficient solution ([Greenslade Interview, Berry Interview](#)). Some experts also mentioned that ORS product design is often not conducive to acceptability, due to taste or ease of use ([Greenslade Interview, Berry Interview](#)). Additionally, experimental evidence shows caregivers are sensitive to price ([Wagner et al., 2019](#)).
- **Provider behavior:** In many countries, provider behavior may contribute to low ORS and zinc usage. For instance, studies in India and Sub-Saharan Africa have suggested that private providers frequently fail to prescribe ORS ([Taneja et al., 1996](#); [Sood & Wagner, 2014](#); [Wagner Interview](#)).
- **Lack of big funder attention:** Some experts suggested that despite big efforts from major funders until the mid-2010s, attention from these players has moved to neonatal and maternal care, drying up funding and interest in

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<sup>3</sup> “The most significant proof of ORT effectiveness came from desperate circumstances during the Indo-Pakistani War in 1971. The conditions of war, complicated by the monsoon season, displaced millions of people into refugee camps, which ultimately led to disastrous cholera outbreak. Early during the outbreak almost 30% of the afflicted patients died due to the shortage of the IVT therapy. Pressed by the disastrous circumstances, Dr Dilip Mahalanabis decided to start providing bags of salt and sugar dissolved in water to the people in the camp. The decision by Dr Mahalanabis proved to be the right one: in just a few months the case-fatality ratio from cholera and cholera-like diarrheal diseases fell below 4% among the people treated with ORT, as compared with the 30% ratio observed previously. This success was a major stepping stone for wider adoption of ORT.” ([Dadonaite, Ritchie, & Roser, 2018](#))



implementing ORS interventions. ([Wagner Interview](#), [Greenslade Interview](#), [Berry Interview](#)).

**Co-packaged ORS and Zinc were added to the WHO Essential Medicines List in 2019, recognizing the benefits of distributing both key diarrhea treatments simultaneously.** This recent development may have opened a window of opportunity for increased work in distributing and promoting ORS and Zinc co-packs.

**Our focus on ORS and zinc does not dismiss the relevance of preventative measures.** However, the academic literature and experts we consulted suggest that while progress in prevention is important, treatment scale-up in ORS and zinc is a well-evidenced and cost-effective intervention that will prevent thousands of deaths. At the same time, preventative measures should be scaled up ([Wagner Interview](#), [Greenslade Interview](#), [Berry Interview](#)). Considering vaccination strategies, [Gill et al. \(2013\)](#) write: “if the global uptake of rotavirus vaccines matched that of the DPT vaccines, an estimated 2.6 million child deaths could be prevented in a 20-year period (roughly 189,000 deaths per year). With the assumption that vaccines could be delivered equitably, which is probably optimistic, all-cause under-5 mortality could be reduced by about 2% (...) the combination of oral rehydration solution and zinc could avert an estimated 75% of diarrhoeal deaths, reducing overall under-5 mortality by 20%” (p.1496).

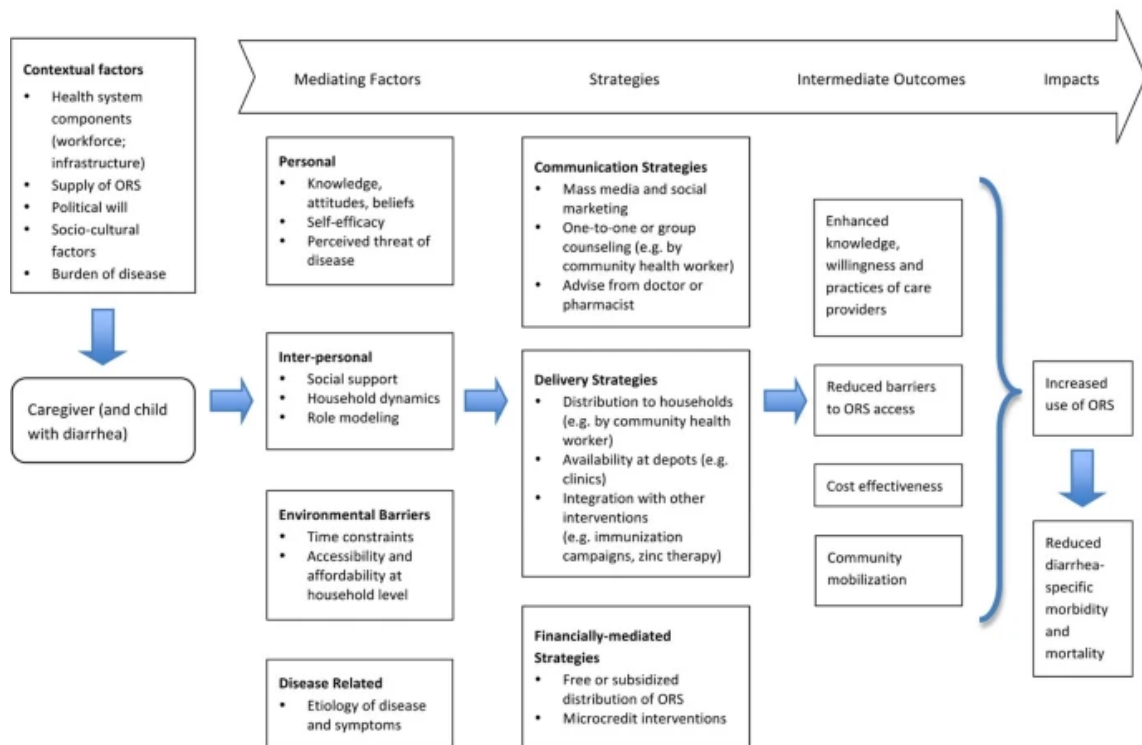
## Theories of change

**A new nonprofit organization could aim to increase the proportion of children with diarrhea treated adequately with ORS and zinc. To achieve this, caregivers must have ready access to ORS and zinc, and be convinced of its benefits.**

Depending on the local contextual reasons for ORS and zinc underuse, an organization working to increase treatment could follow one of several strategies:

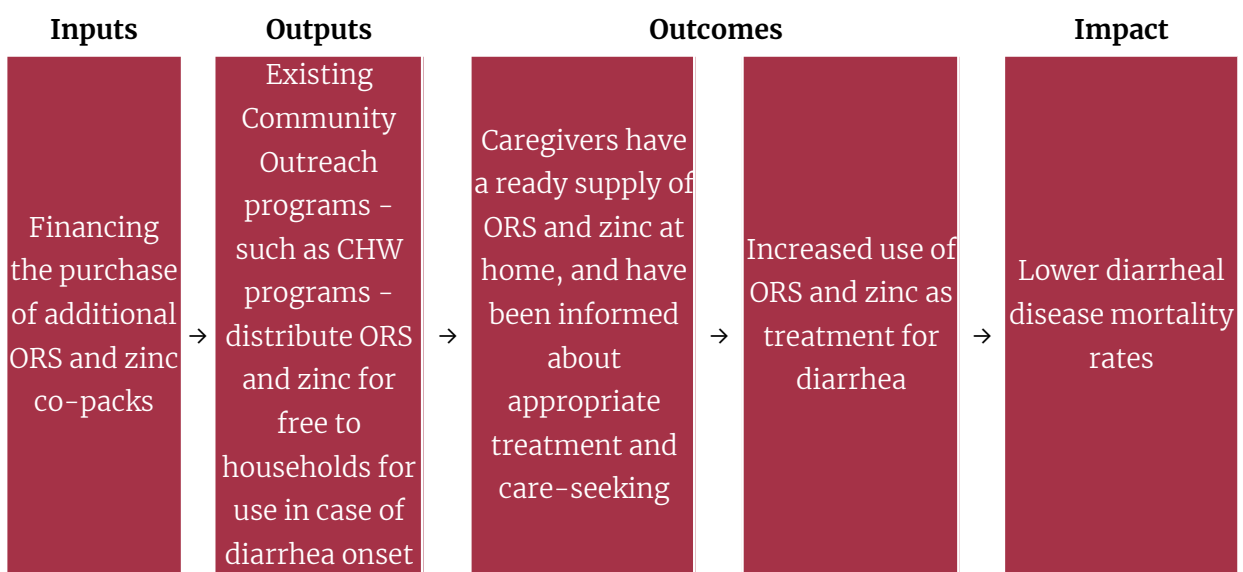
- Working with local producers, health officials, and other stakeholders to improve product design and awareness of ORS and zinc as effective treatments for diarrhea, to catalyze a local industry of ORS and zinc ([Berry Interview](#); [Ramchandani et al., 2022](#)).
- Creating a social entrepreneurship model where individuals sell ORS and zinc to caregivers ([Wagner et al., 2019](#); [Wagner, 2017](#); [Bishai et al., 2015](#)).
- Conducting marketing and behavior-change activities to alter caregiver perception of ORS and zinc, so that they request ORS and zinc from healthcare providers when seeking care ([Wagner Interview](#)).
- Changing healthcare provider perceptions of what caregivers believe is an effective treatment ([Wagner Interview](#)).

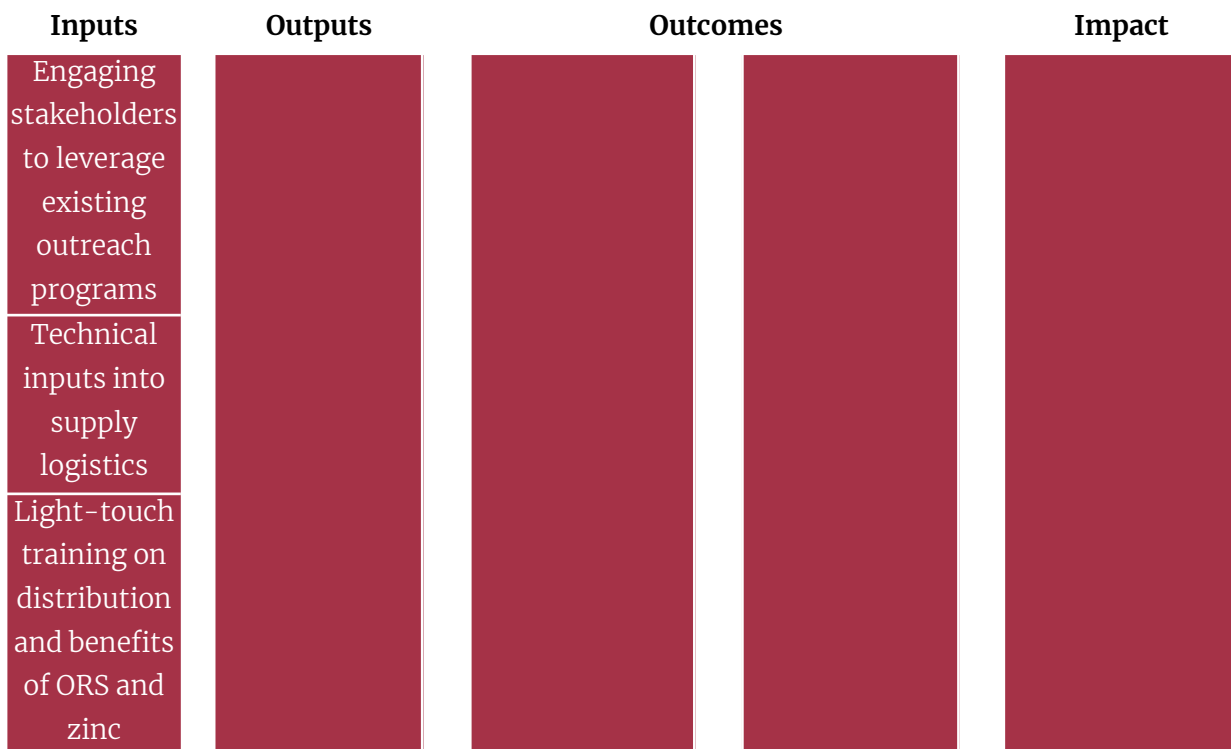
**Figure 1: Conceptual map of interventions to increase ORS use (From [Lenters, Das & Bhutta, 2013](#))**



We mainly focus on a model whereby a charity identifies a health or community outreach program, usually with Community Health Workers (CHWs), and leverages the program to distribute ORS and zinc for free to caregivers ([Wagner et al., 2019](#); [Wagner, 2017](#)). We think that this approach is the most evidenced one. However, charity founders may find opportunities to conduct other strategies while remaining cost-effective.

**Figure 2: Theory of change (ToC)**





The key assumptions corresponding to each step (i.e., “→”) in the theory of change are shown in figure 3.

**Figure 3: Key assumptions in ToC**

<p>A charity can leverage existing community outreach programs. We are moderately confident this is feasible.</p> <p>Sufficient technical knowledge of distribution. We are confident this is feasible.</p> <p>Ability to procure ORS and zinc from manufacturers (local/international). We are confident this is feasible.</p>	<p>CHWs actively distribute the product. We are confident that many CHWs would follow the program guidelines; in our model we account for 60% efficacy, however.</p> <p>CHWs can accurately communicate when and how to use ORS and zinc. We are confident this will not be a key barrier, based on the ease of use of ORS and zinc and the lack of danger in misuse.</p>	<p>When caregivers have ORS and zinc in their home, are given the products for free, and have received information on their benefits, they will treat their children with them. We are moderately confident this is the case.</p>	<p>We are moderately confident that increased treatment rates will lower diarrheal disease mortality rates. There are some uncertainties about the true effect, but there is significant consensus on the historical role of ORS therapy in reducing mortality to current rates.</p>
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Scale: key uncertainty, high uncertainty, some uncertainty, low uncertainty, unconfident

## Geographic assessment

The geographic assessment was done in two stages. First, we looked at where existing organizations are working, or have worked. This information was used as input in the formal geographic assessment to measure how much attention an issue is being paid. Second, we conducted a formal geographic assessment to find the top priority countries for starting a new nonprofit.

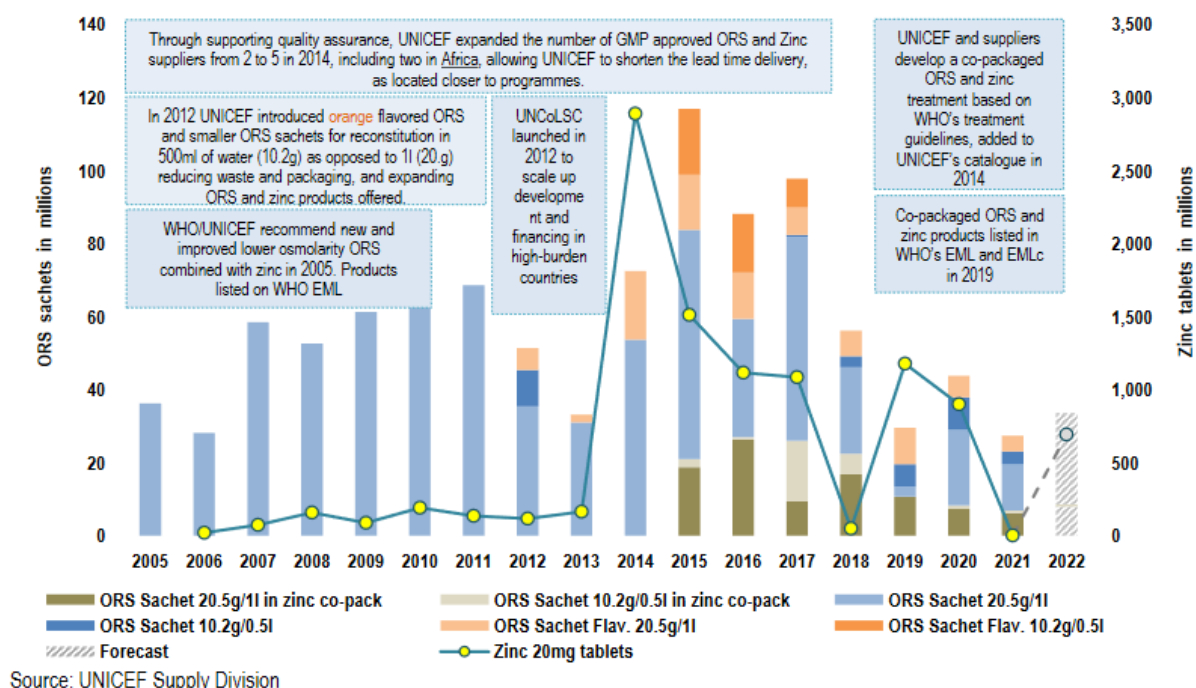
### Where existing organizations work, and the status of ORS and zinc in high-burden countries

**ORS and zinc interventions are usually run as part of more extensive nutrition or diarrhea programming.** Smaller organizations that are more narrowly focused on ORS and zinc distribution have been harder to find, except for [ColaLife](#), an NGO set up to catalyze ORS and zinc co-packaging in Zambia, which handed off operations to for-profit producers and the government in 2018. Experts we consulted suggested that very few (if any) organizations narrowly focus on ORS and zinc distribution ([Ezezika Interview](#), [Berry Interview](#)). USAID, Clinton Health Access Initiative (CHAI), Population Services International, and BRAC have run programs to scale up ORS in the past ([Wagner Interview](#), [Greenslade Interview](#), [Berry Interview](#), [Goh and Pollack, 2016](#)).

Several advocacy, knowledge-sharing, and financing initiatives support ORS and zinc scale-up. For example:

- [The ORS and zinc Co-packaging Alliance \(ORSZCA\)](#) – a global informal network producing resources on and advocating for ORS and zinc co-packaging.
- The World Bank’s Global Financing Facility (GFF) has included [a target to reach 458 million additional children](#) with ORS and zinc by 2025.<sup>4</sup>
- PATH’S [DefeatDD](#), an advocacy group “to raise awareness of the burden of diarrheal disease and help increase access to the solutions.”
- The [United Nations Children’s Fund \(UNICEF\)](#) is a significant procurer and facilitator of ORS and zinc. Its Market & Supply Summary for September 2022 suggests that most ORS supply flows through country and emergency response programs, noting that country demand through UNICEF procurement remains low ([UNICEF, 2022](#)).
- The [Global Fund](#) has also [expanded its strategy](#) to include diarrhea treatment, particularly by funding CHW and integrated Childhood Case Management programs.

**Figure 4: UNICEF ORS and zinc supply 2014–2021 (From [UNICEF, 2022](#))**



<sup>4</sup> GFF eligible countries: Afghanistan, Ethiopia, Malawi, Senegal, Bangladesh, Ghana, Mali, Sierra Leone, Burkina Faso, Guatemala, Mauritania, Somalia, Cambodia, Guinea, Mozambique, Tajikistan, Cameroon, Haiti, Myanmar, Tanzania, Central African Republic, Indonesia, Niger, Uganda, Chad, Kenya, Nigeria, Vietnam, Côte d’Ivoire, Liberia, Pakistan, Zambia, Democratic Republic of Congo, Madagascar, Rwanda, and Zimbabwe.

## Geographic Assessment

The [geographic assessment](#) was conducted considering countries with over 100 total deaths in children under five years old due to diarrheal diseases in the Global Burden of Disease 2019 study ([Global Burden of Disease Collaborative Network, 2019](#)). This assessment included a weighted consideration of the following factors:

### Burden

**We created summary scores reflecting the burden of diarrhea on each country, relative to the rest.** The factors included: the number of deaths due to diarrheal disease (~26% of the overall geographic assessment score), the mortality rate due to diarrhea per 100,000 deaths (~13%), the prevalence of diarrhea per 100,000 in the population (~13%), the rate of change in the mortality rate due to diarrhea between 2010 and 2019 (~2%), the 2028 forecast of the mortality rate due to diarrhea (~3%).

**We also included scores for the treatment of diarrhea** ([UNICEF, 2023](#)), including the proportion of cases of diarrhea in children receiving ORS (~13% of the overall geographic assessment score), and cases of diarrhea receiving ORS and zinc (~13%).

### Tractability

**We constructed a score capturing how difficult it would be to start a charity in the location** (~13% of the overall geographic assessment score). We used an average of how countries compared to others in available scores, in indicators such as the [Fragile States Index](#) and the [World Justice Project Rule of Law Index](#).

### Neglectedness

**A score capturing how much attention ORS and zinc (or diarrhea, in general) are getting, relative to other countries** (~5% of the overall geographic assessment score). For instance: a country's Gross National Income as a proxy for country wealth (~25% of the neglectedness score), being GFF eligible (~25%), the status of ORS and zinc co-packs in a country's essential medicines list [[ORSZCA, 2022](#)] (~12%), and whether the country is eligible for GAVI, the Vaccine Alliance's rotavirus vaccine scale-up program (~37%).

We used subjective weights to arrive at a sensible list of potential countries to work in. For instance, we prioritized tractability to avoid prioritizing countries that would prove extremely difficult to work in. Additionally, we capped the score for the number of under-five-year-old deaths due to diarrhea at a lower maximum than the rest of the scores, to moderate for a country's size.

**Based on this assessment, the ten countries we believe could be prioritized are**

Chad, Niger, Togo, Cameroon, the Central African Republic, Madagascar, Nigeria, Somalia, Yemen, and Burundi.<sup>5</sup>

**Table 1: Summary statistics for top ten priority countries**

Country	Deaths due to Diarrhea ( )	% of children under 5 who received ORS as treatment for diarrhea ( )	Number of children with diarrhea untreated with ORS (2017) ( )
Chad	250,588.81	17.4	170,743
Niger	229,753.32	40.8	112,710
Togo	4,191.83	13.6	37,044
Cameroon	13,471.73	17.9	160,000
Central African Republic	5,409.36	23.4	25,220
Madagascar	10,970.43	19.6	168,806
Nigeria	132,554.90	40	696,169
Somalia	9,530.65	13.2	65,886
Yemen	5,949.74	25.3	271,780
Burundi	5,644.82	35.6	40,223

## A note on the assessment

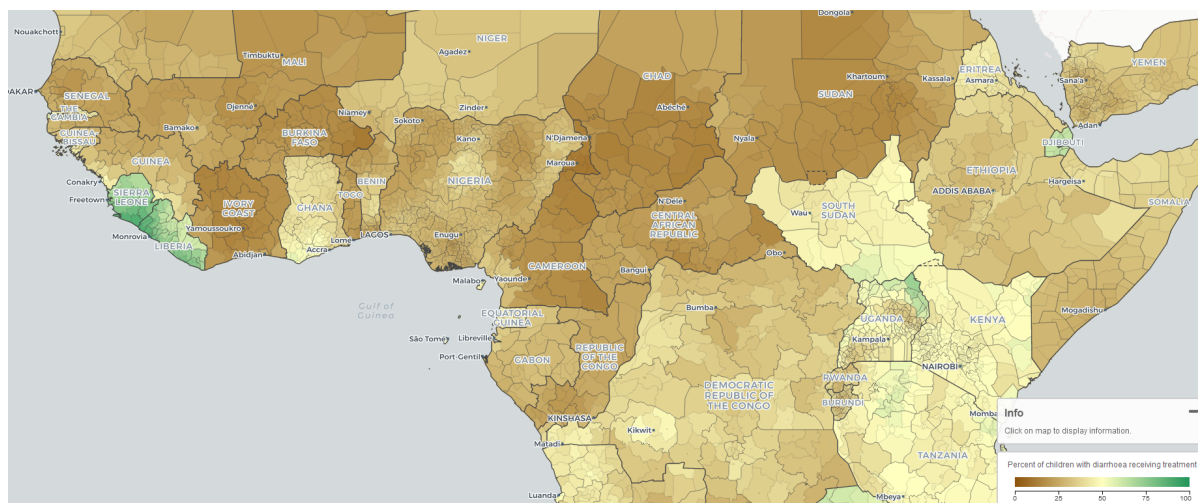
**Investigating sub-national trends using a similar assessment would be a better targeting strategy.** This is because it seems like, in some countries, patterns of diarrheal mortality and ORS and zinc treatment rates are very disparate at the sub-national level and when comparing urban and rural populations. A study on the local burden of diarrhea in 2017 found that Afghanistan, Benin, Cameroon, Democratic Republic of the Congo, Colombia, Ethiopia, Guinea, Jordan, Nigeria, Sudan, and Uganda “had at least 50% relative deviation in one of their [administrative] units in ORS use in 2017” ([Local Burden of Disease Diarrhoea](#)

<sup>5</sup> Jane Berry, of ColaLife and ORSZCA, has pointed out that many of these countries are french-speaking. When collating resources on ORS and Zinc, ORSZCA found a dearth of resources in the french language. ORSZCA has translated all their resources and are actively trying to reach more francophone countries.

[Collaborators, 2020, e1043](#)).<sup>6</sup> We return to this discussion in the [cost-effectiveness section](#).

Experts were somewhat surprised that countries with large burdens, such as India, Ethiopia, and Pakistan, were not on the list, which may be worth exploring.

**Figure 5: Percentage of children under 5 receiving ORS treatment, 2017 (From Institute for Health Metrics and Evaluation (IHME), 2020)**



Considering these factors, **we advise refining the assessment** by using indicators such as local levels of ORS and zinc treatment, as estimated in the Local Burden of Disease ORT study ([Institute for Health Metrics and Evaluation \(IHME\), 2020](#)); [local patterns](#) in diarrhea mortality; community health worker per population; and levels of treatment in rural vs. urban settings.

## Quality of evidence

### Evidence that a charity can make a change in this space

In this section, we discuss the evidence from past efforts to increase treatment rates. Several countries and programs have reached strong levels of treatment through a combination of demand and supply interventions and – often – concerted government action.

#### Free preemptive delivery by Community Health Workers

#### **One potential strategy for increasing ORS and zinc use involves using existing Community Health Worker (CHW) programs to conduct free preemptive delivery**

<sup>6</sup>“In 2015, Nigeria had the largest difference observed in the within-country mortality rates, with first-level administrative subdivisions differing by a factor of 6; estimates ranged from 1.6 deaths (95% credible interval, 1.0 to 2.3) per 1000 children in the Bayelsa region to 9.5 deaths (95% credible interval, 7.1 to 12.8) per 1000 children in the Yobe region.” ([Reiner et al., 2018](#))



**of ORS and zinc co-packs.**<sup>7</sup> Experts were generally supportive of this intervention ([Wagner Interview](#)).

**The best evidence regarding this intervention comes from a randomized controlled trial conducted in Uganda** ([Wagner et al., 2019](#); [Wagner, 2017](#)). CHWs were instructed to deliver ORS and zinc tablets to all households with under five-year-olds, and provide standard information about their treatment use. Compared to the control (a standard entrepreneurial program where CHWs visit households and sell subsidized health commodities), delivering ORS and zinc for free to caregivers increased ORS treatment by 20 percentage points – by 36% – and ORS+zinc by 33 percentage points – by 106%. Notably, “only 60% of households received the free home deliveries, suggesting that usage could be improved further with better CHW adherence.” ([Wagner et al., 2019, p.12](#)). Additionally, the effect was stronger in villages with lower baseline treatment rates.

**Another cluster randomized controlled trial studied an entrepreneurial model for CHWs, where CHWs treat a few common illnesses at the household level and sell subsidized goods.** In this case, ORS and zinc treatment levels in intervention sites were slightly higher than in control (adjusted risk ratio 1.16, 38% vs. 33%) ([Björkman Nyqvist et al., 2016](#)). Both RCTs suggest that increasing ORS treatment with CHWs is feasible, yet a free distribution intervention would have a larger effect.

**A qualitative review of successes and failures in ORS scale-up suggests that countries like Guyana became a “sustained success” in ORS scale-up due to awareness raising through marketing campaigns, and distribution through a network of CHWs that made ORS free and readily available.** Malawi (where nowadays over 60% of children are treated with ORS), with help from USAID and Population Services International, made ORS universally recognized and free in the public sector ([Wilson et al. 2013](#)).

**CHW programs are relatively common in low-resource countries, especially in Sub-Saharan Africa** ([Wagner Interview](#)). Evidence from other CHW programs for other diseases and strategies (such as preventative strategies) may provide an approximate sense of the potential of this intervention. A Cochrane review of lay health worker programs results suggests moderate-quality evidence that these workers can improve Tuberculosis outcomes, exclusive breastfeeding, and immunization uptake ([Lewin et al., 2010](#)). Another systematic review focused on low- and middle-income countries found moderate evidence that CHWs effectively deliver preventative interventions ([Gilmore & McAuliffe, 2013](#)).

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<sup>7</sup> Please note that while we mostly focus on CHWs in this report, we think that many other outreach or door-to-door programs could be suitable for this type of intervention.

## Co-promotion of ORS and zinc

**There is moderate/low-quality evidence that promoting zinc alongside ORS increases the use of ORS.**

**A systematic review and meta-analysis of this strategy suggest that caregivers who receive this intervention are 1.82 times (95% CI 1.17 - 2.85) more likely to give their infants ORS.** This evidence comes from four randomized controlled trials, yet is biased toward South Asia, and the effects are dominated by one of the studies ([Lenters, Das & Bhutta, 2013](#)).

**ColaLife have suggested that in their experience, zinc pills give a more “medicinal” appearance to ORS and zinc co-packs, leading to caregiver approval** ([Berry Interview](#), [Goh and Pollack, 2016](#)). This was part of the evidence and rationale in their advocacy for the co-pack to be placed on the WHO essential medicines list. An expert with clinical experience in Uganda agreed that zinc co-promotion might bolster ORS treatment rates ([Laing Interview](#)).

## Demand-generation of ORS and zinc

There is some evidence that strategies to raise awareness of ORS and zinc can change ORS usage. Usually, these strategies are deployed in combination with increased distribution.

**Some observational studies have shown increases in the use of ORS after exposure to knowledge interventions.** In their meta-analysis, [Lenters, Das, and Bhutta \(2013\)](#) found that exposure to these interventions increased the chance of ORS treatment by 2.05 (95% CI 0.78, 5.42). However, this meta-analysis effect was not statistically significant.

**Other studies and experts** ([Berry Interview](#), [Ezezika Interview](#)) **suggest that demand generation and awareness raising may have supported gains in ORS and zinc treatment.** Some approaches have included community-based, awareness-raising activities and the use of community health advocates or champions. Some successful case studies, like the successful expansion of ORS in Bangladesh through community health promotion volunteers ([Cash, 2021](#)), suggest that correct messaging may support ORS uptake ([Goh and Pollack, 2016](#)). [Wilson et al. \(2013\)](#) note that in Sierra Leone, a successful scale-up strategy took advantage of the displacement caused by civil war, given that ORS was heavily promoted in displacement camps where more than a third of the country’s population was found. ColaLife worked from the early 2010s until 2018 in Zambia, and seemed to have contributed to reaching ~65% coverage rates of ORS and 35% coverage of ORS and zinc (Berry Interview). Co-packaging played a key role in ORS and zinc coverage in Zambia (Berry interview).

**Mass-media strategies are relatively inexpensive, so they pose promise if effective.** The evidence that mass-media interventions have affected ORS and/or zinc use is very low quality, coming from observational studies. A multi-pronged intervention study by CHAI in Gujarat and Uttar Pradesh suggests that mass media interventions may have an “amplifying” effect when paired with other interventions (in this case, high-frequency training with providers) ([Lam et al., 2019](#)).<sup>8</sup>

**Demand generation can work by changing healthcare provider prescription practices.** In an upcoming RCT study, Wagner et al. (upcoming) show that caregivers who expressed a preference for ORS doubled ORS prescription rates and reduced the provision of antimicrobials ([Wagner Interview](#)). This experimental evidence has not been reviewed exhaustively, but suggests that providers respond to patient preferences.

**Finally, product design and supply chain support may also be potential avenues for innovation.** ColaLife and other NGOs have worked to improve product design to satisfy caregiver preferences. Experts see this as a potential way to generate excitement and trust in ORS and zinc as diarrhea treatment ([Berry Interview](#), [Goh and Pollack, 2016](#), [Greenslade Interview](#), [Ramchandani et al., 2022](#)). We could not find high-quality studies that address these claims.

## Evidence that the change has the expected health effects

**The WHO recommends treating diarrhea with ORS and a 10 to 14-day course of supplementary zinc.** Co-packaged ORS and zinc were added to the model essential medicines list in 2017. In this section, we focus on the mortality effects; other effects are noted in the cost-effectiveness section.

**The best evidence of the effect of ORS on mortality comes from a systematic review and meta-analysis ([Munos, Fischer Walker, & Black, 2010](#)).** It suggests that **ORS may prevent 93% of diarrhea deaths at 100% coverage.** A Cochrane review comparing oral vs. intravenous rehydration in children with gastroenteritis suggests no clinically significant differences in outcomes ([Hartling et al., 2006](#)).

Observational studies have also demonstrated drastic reductions in deaths when ORS was used ([Dadonaite, Ritchie, & Roser, 2018](#)).

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<sup>8</sup> [Goh and Pollack \(2016\)](#) cite several other instances of mass media being used. For instance, “in Senegal, MI supported the MoH to launch a national, multi-media campaign to increase zinc and ORS use. The campaign included three radio spots, a traditional song, and one TV spot in local languages. After eight months of implementation, care-seeking for diarrhea outside of the home increased from 42% (baseline) to 52% (endline). In addition, awareness of ORS and zinc increased among non-users from 18% to 51% for ORS and 5% to 32% for zinc” (p.38)

**However, there are significant uncertainties about the real mortality effect of increases in ORS at scale** ([Wagner Interview](#)). GiveWell points out a few: it is unclear whether the quality of treatment given by caregivers is equal to that administered by professionals, whether treatment frequency and dosage changes are effective, and whether ORS is similarly effective when homes have no access to safe drinking water ([GiveWell, 2021](#)).

**The mortality effects of zinc supplementation on diarrhea are less clear.** [Fischer Walker and Black \(2010\)](#) estimate that zinc supplementation leads to a 23% mortality reduction by utilizing hospitalizations as a proxy. They point out that given the evidence on the benefits of zinc, it is no longer ethical to conduct RCTs on their effect. [Black et al. \(2019\)](#) attribute a 2.9% reduction in deaths due to diarrhea between 2015 and 1980 to zinc supplementation coverage increases.

**The best evidence available (from high-quality RCTs) on zinc supplementation suggests that zinc supplementation (compared to ORS alone) can shorten the duration of prolonged diarrhea by a third and “may prevent future diarrhoeal episodes in the 2–3 months following supplementation”** ([Fischer Walker and Black, 2010](#)). A Cochrane review of the intervention has similar conclusions, noting that zinc may shorten the duration of persistent diarrhea by 16 hours, and acute diarrhea by half a day in children older than six months ([Lazzerini & Wanzira, 2016](#)). It is difficult to disentangle the effect of zinc from ORS on mortality, given a lack of studies where these were not given together.

## Expert views

We conducted three in-depth interviews with relevant experts at this research stage.

- **Dr. Zachary Wagner**, Economist & Professor of Policy Analysis at the Pardee RAND Graduate School and author of numerous studies on ORS ([Wagner Interview](#))
- **Simon Berry OBE**, founder and CEO of ColaLife and co-founder of the ORS/Zinc Co-pack Alliance (ORSZCA) secretariat (Berry Interview)<sup>9</sup>
- **Leith Greenslade**, coordinator of the Every Breath Counts Coalition and special adviser to ORSZCA (Greenslade Interview)

We also contacted two experts in the previous stage, and discussed diarrhea treatment with a third during consultations for another report.

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<sup>9</sup> We also thank Jane Berry (co-founder and business development director, ColaLife) for her written comments and contributions in the interview.

- **Dr. Obidimma Ezezika**, Assistant Professor, University of Toronto and author of a systematic review on barriers and facilitators to ORS scale-up (Ezezika Interview)
- **Saul Morris**, Director of Programme Services at the Global Alliance for Improved Nutrition (Morris Interview)<sup>10</sup>
- **Dr. Nicolas Laing**, Executive Director at One Day Health and Clinical Practitioner in Northern Uganda ([Laing Interview](#))

**Most experts supported that a charity should start in this space**, suggesting that areas with high numbers of deaths and diarrheal disease prevalence should be a priority. There is also considerable expert consensus on ORS and zinc as major tools in the fight against diarrheal disease ([The Lancet, 1978](#); [Nailin & Cash, 2018](#)). One expert suggested that diarrheal disease prevention should take priority over ORS use.

**Experts noted that although significant attention was given to ORS scale-up until the mid-10s, major funders in global health have moved on to other priorities.** The lack of funding in the ORS space was a major theme in some conversations, with experts noting that accessing funds for such a charity may be difficult. Simon Berry pointed out that the major global funding streams currently are GFF and GF, which go to governments. However, most governments work in partnership with NGOs, and there are some other funding sources available (Berry Interview).

**There was a prevailing sense that ORS scale-up is a comparatively easy intervention, given that the commodities involved are cheap, accessible, and do not require complex transportation systems (such as cold chains).**

**There was agreement that both supply and demand strategies could prove effective.** Some experts strongly support “total market” or holistic approaches, including wide partnerships and combining a range of interventions ([Shops Plus, 2014](#)). Provider behavior was noted as a major determinant of ORS use and antibiotic misuse. Dr. Walker discussed a recent RCT in two Indian states that demonstrated private providers are responsive to caregiver preferences, showing that demand generation may support ORS scale-up activities by improving prescription practices in the private healthcare sector.

**Several experts noted that local buy-in and engagement would be key, particularly if the aim is to catalyze a local industry.** Free provision of ORS was noted to have negative implications for local manufacturing (as local manufacturers may not be able to compete with imports). Charity founders should consider the benefits and drawbacks of purchasing (or setting up) from local manufacturers.

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<sup>10</sup> These notes are not public by request of the expert.

## Cost-effectiveness analysis

Our [cost-effectiveness analysis](#) models a hypothetical 13-year program of free and preemptive delivery of ORS and zinc to all under-five-year-olds in Chad, Niger, Nigeria, Togo, Cameroon, Madagascar, and Burundi.

**We model the commodity costs of ORS and zinc per treatment, the labor costs of providing treatment, logistics costs, and the costs of managing CHWs.**

**We use current ORS treatment rates in each country and, based on results from Wagner et al. (2019), we model a year-on-year 36% increase in ORS treatment rates** (up to treatment rates of 70%, which we have assumed would be the roof based on the current ORS treatment rates in the best-performing countries in SSA). Our main model only accounts for the mortality effects of ORS, where the evidence is strongest.

**This intervention looks cost-effective, with an average cost-effectiveness of \$188 per disability-adjusted life year (DALY).**<sup>11</sup> Our findings are summarized in table 2.

**Table 2: Cost-effectiveness per country - model 1**

Country	Total cost (USD)	Total number of deaths averted	Total number of DALYs averted	\$/DALY (USD)
Chad	43,289,843	20,641	753,957	57
Madagascar	32,249,375	5,887	215,031	150
Nigeria	290,354,622	46,585	1,701,658	171
Togo	14,186,522	2,180	79,639	178
Burundi	22,900,560	2,783	101,647	225
Cameroon	52,041,107	5,856	213,906	243
Niger	46,044,223	4,309	157,414	293
Average	71,580,893	12,606	460,465	188

**According to the Disease Control Priorities Volume 3, the most cost-effective interventions for diarrhea mortality are zinc supplementation (with or without ORS), ORS, rotavirus vaccines, and household-level water treatment (Keusch, et al., 2016).** ORS seems to enjoy significant expert consensus as a highly cost-effective intervention in diarrhea control.

Below we detail some cost-effectiveness estimates found in our literature review.

<sup>11</sup> "One DALY represents the loss of the equivalent of one year of full health. DALYs for a disease or health condition are the sum of the years of life lost to due to premature mortality (YLLs) and the years lived with a disability (YLDs) due to prevalent cases of the disease or health condition in a population" [Disability-adjusted life years \(DALYs\)](#).

**Table 3: Cost-effectiveness in the literature**

Citation	Intervention	Method	\$/DALY (USD)
<a href="#">Robberstad, et al. (2004)</a>	ORS + zinc provision to all children with dysenteric and non-dysenteric diarrhea in Tanzania	Modeled	73
	Adding zinc to the ORS-only treatment of all children with dysenteric and non-dysenteric diarrhea in Tanzania	Modeled	11
<a href="#">GiveWell (2021)</a>	ORS scale-up	Modeled	153 <sup>12</sup>
<a href="#">Wagner et al. (2022)</a>	“Free distribution of oral rehydration salts (ORS) via home deliveries prior to diarrhea onset (free delivery arm)” in Uganda	RCT	56
<a href="#">Bishai et al. (2015)</a>	A social franchising intervention in 3 townships of Myanmar in 2010, to promote an ORS-zinc product	Modeled based on program outcomes	214

## Effects

**To understand the potential effect of scaling up ORS and zinc usage, we drew on data on the burden of diarrheal disease (incidence and death), current levels of treatment with ORS, and the size of the population under five years old.**

The mortality effect used for ORS was 93% ([Munos, Fischer Walker, & Black, 2010](#)). According to LiST, the proportion of diarrhea cases that can be affected by this intervention is 88%. We discount the impact of this intervention by assuming that only 60% of CHWs deliver the ORS and zinc co-packs, as was the case in [Wagner et al., 2019](#). We also use other subjective judgments, including the overall probability of success of the charity (80%), and a discount rate of 4% for future effects and costs.

**There are some reasons to believe that the effects of this intervention could be larger than is currently being modeled in our main model:** we do not include any morbidity effects due to shorter diarrhea cases or lower recurrence rates, which according to some studies may have a substantial DALY burden;<sup>13</sup> we do not include

<sup>12</sup> Cost per under-5 death averted \$5,591 / 36.528 (DALY value of under 5 year old death averted).

<sup>13</sup> “Diarrhoea episodes are significantly associated with childhood growth faltering. We found that each day of diarrhoea was associated with height-for-age Z-score ( $-0.0033$  [95% CI  $-0.0024$  to  $-0.0041$ ];  $p=4.43 \times 10^{-14}$ ),

any mortality benefits from zinc supplementation, to avoid double counting; and we only count direct mortality due to diarrhea – many deaths occur for more than one reason (e.g., pneumonia and diarrhea) which means that we are probably undercounting the mortality effect of diarrhea.

## Costs

**To understand costs, we mainly rely on LiST and the WHO costing guidance through their [cost-effectiveness tools](#).** We used the same fixed costs across interventions for this global health round of research. For variable costs, we include

- The cost of ORS and zinc co-packs (~USD 0.4/treatment)
- The cost of paying CHWs for each treatment (~USD 0.04/treatment, assuming that most households have many children in them)
- Full-time employees (CHW managers)
- A 30% markup on per/treatment costs for logistics

## Alternative models

### Model 2 – Yobe, Nigeria

To test whether more targeted approaches at the sub-national level would yield improved cost-effectiveness. We used model 1 and targeted one of the most burdened areas in Sub-Saharan Africa, **Yobe State in Nigeria**.

We used estimates from [Reiner et al. \(2018\)](#) for the mortality rate in the state. We calculated the incidence using the ratio at the national level (the real incidence in the state is likely larger, as the incidence in Yobe is known to be far more burdened than the Nigerian average). Still, we could not find an equivalent incidence.

We use estimates of ORS coverage from [Local Burden of Disease Diarrhoea Collaborators \(2020\)](#). The coverage of ORS in Yobe, according to this source, was ~22% in 2016.

**The cost-effectiveness of the same 13-year program from the first model, conducted in Yobe, yields a ~47 USD/DALY ratio, similar to the estimate for Chad.**

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weight-for-age Z-score ( $-0.0077$  [ $-0.0058$  to  $-0.0097$ ];  $p=3.19 \times 10^{-15}$ ), and weight-for-height Z-score ( $-0.0096$  [ $-0.0067$  to  $-0.0125$ ];  $p=7.78 \times 10^{-11}$ ). After addition of the DALYs due to the long-term sequelae as a consequence of undernutrition, the burden of diarrhoeal diseases increased by 39.0% (95% uncertainty interval [UI] 33.0–46.6) and was responsible for 55 778 000 DALYs (95% UI 49 125 400–62 396 200) among children younger than 5 years in 2016. Among the 15 652 300 DALYs (95% UI 12 951 300–18 806 100) associated with undernutrition due to diarrhoeal episodes, more than 84.7% are due to increased risk of infectious disease, whereas the remaining 15.3% of long-term DALYs are due to increased prevalence of protein energy malnutrition.” ([Troeger et al., 2018](#))



### Model 3 – lower costs and morbidity adjustments

Finally, we model a third option. We make two changes to the initial model:

- **Costs.** It is plausible that a new charity could leverage the resources of an existing outreach program and simply add the commodities, management, and logistics capacity. We, therefore, consider a model in which a charity hires managers (one per 20,000 cases), but does not spend anything else on labor.
- **Morbidity.** There is considerable evidence that diarrhea has a large disability burden ([Troeger et al., 2018](#)) and that ORS and zinc also have morbidity effects (see [evidence section](#)). We adjusted the DALYs averted by 15% to reflect this burden.

**With these adjustments, the resulting average cost-effectiveness is USD 121/DALY (min: USD 35; max: USD 209).**

### Illustrative LiST projections

We also conducted a rapid Lives Saved Tool (LiST) analysis to understand how the model projects the mortality effects of ORS and zinc upscaling.

**Using LiST allows us to check the projected cost-effectiveness with a different model.** Note, however, that these are not directly comparable to our modeling – for instance, in the LiST model, 50% of cases are treated in the community and the other 50% in hospitals. We model the mortality effects of a linear increase from the status-quo treatment in ORS and zinc up to 60% from 2023 to 2027.

Country	Lives Saved - ORS	Lives Saved - zinc	Cost (USD)	Cost/Life Saved	Cost/DALY (USD)
<b>Chad</b>	11,483	2,636	37,368,290	2,647	73
<b>Niger</b>	4,865	2,606	46,184,846	6,182	171
<b>Nigeria</b>	67,482	18,549	656,008,269	7,625	210
<b>Togo</b>	1,269	341	10,831,254	6,727	186
<b>Cameroon</b>	6,391	1,473	60,929,108	7,748	214
<b>Madagascar</b>	4,245	1,207	32,300,303	5,924	163
<b>Burundi</b>	1,502	538	14,958,412	7,333	202
			<b>Average</b>	5,435	150

## Implementation

### Talent

Scaling up ORS and zinc co-packs for the treatment of diarrhea in under five-year-olds **is not a prohibitively complex area, and operationally the intervention is relatively simple**, so it should not be difficult to find talent capable of working on this issue. This is not a highly technical intervention, and thus a healthcare background is a preferred but not disqualifying requirement.

We believe a few “nice-to-haves” exist in an ideal co-founder for this intervention. The following expertise profiles could be helpful: **in-country experience, ideally with health stakeholders (particularly manufacturers and CHWs), marketing, health commodity design, and supply chain/logistics**. Some experts noted a need for innovation in product design to support treatment upscaling, by tailoring the product to caregiver preferences.

### Access

#### Information

**We do not expect access to information to be a barrier.** Several groups are interested in supporting scaling up ORS (e.g., ORSZCA, ColaLife, DeafeatDD) and share extensive resources on implementation online (e.g., the [ColaLife playbook](#)). Health surveys frequently ask about ORS and zinc treatment, and there is decent (though sometimes outdated) information on treatment levels online.

Relevant stakeholders:

**Experts view stakeholder engagement and coordination as the main facilitator for these interventions.** If the new non-profit uses the free and preemptive delivery model relying on CHWs, then relationships with ministries of health or NGOs implementing those programs will be key.

**ColaLife reported that in their context, stakeholders were generally in favor and eager to support their work** ([Berry Interview](#)). It will be important to coordinate with relevant ministries of health, commodity producers, and potentially other NGOs where CHW programs are not state-run.

### Feedback loops

Many forms of RCTs involving ORS or zinc to understand mortality effects would be unethical. **Likely, some uncertainties around the ultimate mortality effect of the**

**ORS scale-up remain unanswered without high-quality evidence.** However, it should be **relatively straightforward to monitor ORS and zinc treatment rates** and run moderate/high-quality studies where needed. This would be helpful to understand some outstanding uncertainties regarding how plausible it is to increase ORS and zinc use, and what current determinants of ORS and zinc use look like.

## Funding

### Effective Altruism organizations' funding

Experts noted that funding for ORS and zinc is more constrained than in other global health areas, such as maternal or neonatal mortality. **An expert mentioned that GiveWell has shown interest in ORS**, and is potentially looking to develop research to resolve some of its uncertainties.

### Funding in Global Health

ORS and zinc are proven and cheap interventions. However, **experts noted that accessing funding can be challenging, as funders prefer more comprehensive programs**. The major players in the field may prioritize prevention, and other areas such as maternal and neonatal health.

## The scale of the problem

Despite being a proven intervention, **ORS coverage rates have stalled at around an average of 40% of diarrhea cases treated** ([Khan, Wright & Bhutta, 2020](#); [Dadonaite, Ritchie, & Roser, 2018](#)). In some high-burden countries, treatment with ORS can be as low as 13.6% ([World Bank, 2023](#)). Therefore, there are many countries that a new charity could scale to. However, it is important to highlight the findings of our cost-effectiveness analysis. Whilst there seem to be extremely cost-effective areas to target work, cost-effectiveness appears to diminish when scaling to other countries.

We expect free preemptive delivery of ORS and zinc co-packs by CHW to be an easily scalable intervention that should be **replicable between countries**. However, we do note that if you want to include other potential theories of change alongside this intervention, it will be important to take into account the local contextual reasons for ORS and zinc underuse.

## Neglectedness

Our sense is that despite decades of support from experts and prior interest in scaling up ORS and zinc, **it is a neglected intervention**. We base this on stagnant

treatment rates and expert insight. Zinc treatment rates, in particular, are very low. See [funding](#) and [geographic assessment](#) for more.

## Tractability

Our sense is that it is **possible to increase ORS and zinc treatment rates through free and preemptive delivery of ORS and zinc, potentially paired with demand generation and/or industry support**. ORS and zinc are easy to manufacture and transport.

## Externalities

**Antimicrobials are frequently wrongly prescribed for diarrhea** ([Taneja et al., 1996](#); [Sood & Wagner, 2014](#)). There is some evidence from randomized trials that ORS and zinc treatment scale-ups can contribute to lower antimicrobial misuse ([Wagner Interview](#); [Baqui et al., 2004](#); [Awasthi & INCLEN Childnet zinc Effectiveness for Diarrhea \(IC-ZED\) Group, 2006](#)).

**Increasing the effective treatment of diarrhea at home may free up healthcare system resources**. Additionally, there is some evidence that free distribution of commodities (ORS, in this case) motivated CHWs to make more visits compared to entrepreneurial models, where the ORS was sold ([Wagner, Asimwe, and Levine, 2020](#)). This could plausibly mean that the intervention would have the effect of providing extra motivation to CHWs ([Wagner Interview](#)).

**Additionally, it should be noted that diarrhea is a major killer in over 70-year-olds**. Whilst this report focuses on child mortality, it is possible that ORS and zinc scale-ups have a considerable impact on adult mortality if scale-up is achieved in that population.

An expert noted that a negative effect of increasing the treatment of diarrhea at home **could potentially be that caregivers do not seek a diagnosis**. Diarrhea is also a symptom of other diseases, particularly malaria. Whilst this is somewhat a conjecture, it would be warranted for an implementer to monitor adverse effects on care-seeking, based on precaution. ([Laing Interview](#)).

## Remaining uncertainties

For any country, **the actual case fatality ratio (risk of dying) in cases that do not get treated with ORS is not known**. That is, an intervention that increases ORS and zinc use could plausibly be increasing ORS treatment in populations with milder

cases (i.e., where the patient would be unlikely to die). The case fatality ratio for diarrhea varies greatly depending on the pathogen, cause, and other variables (Asare et al, 2022).<sup>14</sup>

However, as experts pointed out – ORS and zinc co-pack treatment should be standard for all cases of diarrhea, due to their protective effect. Diarrhea cases start as mild and can worsen rapidly. Therefore, making sure every child gets treated with ORS and zinc has strong protective effects in expectation, as well as morbidity benefits.

## Conclusion

Overall, our view is that a new charity scaling up the distribution of ORS and zinc co-packs for the treatment of diarrhea in under five-year-olds is an idea worth recommending to future nonprofit founders.

As cheap, highly evidenced, and effective treatments for diarrhea, ORS and zinc should enjoy higher levels of treatment than those achieved in many high-burden countries. We believe that sufficient evidence suggests that concerted attempts to change behaviors and increase access to treatment can yield good results, leading to a large and cost-effective impact on diarrheal mortality and morbidity.

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<sup>14</sup> “When pathogens were included as predictors of the CFR in the overall model, the highest and lowest odds ratios were found for enteropathogenic *Escherichia coli* (EPEC) [odds ratio (OR) = 3.0, 95% CI: 1.28–7.07] and rotavirus (OR = 0.23, 95% CI: 0.13–0.39), respectively.” (Asare et al, 2022)

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