Cost-effectiveness of Zinc Supplementation for Prevention of Childhood Diarrhoea in Tanzania

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Conflict of Interest
None

Authorship
HPS, NM, CD- formulated the research question, designed the study, carried it out literature review, analysed the data and wrote the article. EL, KM, CD-helped with data abstraction, supervised, reviewed initial and subsequent drafts of manuscripts and advised pertinent issues.

Ethical Standards Disclosure
No individual patient data were collected or accessed for the purposes of this study.
Abstract

Objective: To assess the cost-effectiveness of prophylactic zinc supplementation for preventing diarrhoea in young children in Tanzania.

Design: Cost-effectiveness analysis using decision-analytic modelling. Cost-effectiveness ratios were calculated as the incremental cost (2019 USD) per disability-adjusted life year (DALY) averted, from a societal perspective, and with a 3% discount rate applied to future outcomes. Sensitivity analyses were performed to test the robustness of results to alternative assumptions.

Setting: Tanzania.

Participants: A hypothetical cohort of 10,000 children ages 6 weeks to 18 months.

Results: The intervention costs of zinc supplementation were estimated as $109,800 (95% uncertainty interval: 61,716–171,507). Zinc supplementation was estimated to avert 2,200 (776–3,737) diarrhoeal episodes, 14,080 (4,692–25,839) sick days, 1,584 (522–2,927) outpatient visits, 561 (160–1,189) inpatient bed-days, 0.51 (0.15–1.03) deaths, and 19.3 (6.1–37.5) DALYs (discounted at 3% per year). Zinc supplementation reduced diarrhoea care costs by $12,887 (4,089–25,058). The incremental cost per DALY averted was $4,950 (1,678–17,933). Incremental cost-effectiveness ratios (ICERs) estimated from a health system perspective were similar to the results from the societal perspective. ICERs were substantially lower (more favourable) when future outcomes were not discounted, but all ICERs were above contemporary thresholds for cost-effectiveness in this setting.

Conclusion: Prophylactic zinc reduced diarrhoea incidence and associated healthcare utilization; however it did not appear to be cost-effective for prevention of childhood diarrhoea in the scenario examined in this study. Reducing intervention costs, or identifying high risk groups for intervention targeting, may be needed to improve cost-effectiveness in this setting.

Keywords: Diarrhoea, Zinc, Supplementation, Children, Cost-effectiveness, Tanzania
Introduction

Diarrhoea is among the top three causes of death and illness in children under five years of age in Tanzania (Afnan-Holmes et al., 2015). In the 2015-16 Demographic and Health Survey, 12% of children in this age group were reported to have had diarrhoea in the 2 weeks before the survey (Tanzania Ministry of Health, 2016). Malnutrition has been linked to diarrhoea in children, with children suffering from malnutrition at increased risk of diarrhoea due to compromised immunity (Brown, 2003). Diarrhoea can also exacerbate malnutrition, leading to on-going comorbid diarrhoea and malnutrition. Zinc deficiency is common in low-income countries due to poor dietary intake and limited bioavailability, and is associated with increased risk of gastrointestinal infections causing diarrhoea (Walker and Black, 2007; Penny, 2013). Zinc is a vital micronutrient important for protein synthesis, cell growth and differentiation, immune function and intestinal transport of water and electrolytes. It is associated with many other positive health benefits necessary for growth and development (Brown et al., 2009; Yakoob et al., 2011).

Zinc supplements can be given to children therapeutically or prophylactically (Penny, 2013). Zinc and Oral Rehydration Solution (ORS) are the standard for treatment of childhood diarrhoea, as recommended by the World Health Organization (WHO)(World Health Organization, 2017). Several studies have also shown the effectiveness of zinc given to healthy children as a diarrhoea prophylaxis (Brown et al., 2009; Yakoob et al., 2011; Penny, 2013). Despite this evidence, zinc is not currently recommended for childhood diarrhoea prophylactic purposes. Prophylactic zinc could potentially be used alongside rotavirus vaccine to avert childhood diarrhoea, especially among the neediest children with inadequate diet, for whom zinc supplementation might be most beneficial.

In Tanzania, a randomized, double-blind, placebo-controlled clinical trial (NCT00421668) found that daily zinc supplementation was effective in preventing diarrhoea among young children aged 6 weeks to approximately 18 months (McDonald et al., 2015). In this trial, children were randomly assigned to receive daily zinc supplementation or placebo for 18 months, and followed up monthly to determine the effect of zinc on diarrhoea incidence. Prophylactic zinc supplementation was found to reduce the occurrence of all types of diarrhoea (12% reduction, rate ratio 0.88 (0.81-0.96)) and dysentery (16% reduction, rate ratio 0.84 (0.74-0.95)).
There is limited information with regards to the cost-effectiveness of prophylactic zinc supplementation. While a number of studies have examined the cost-effectiveness for preventing diarrhoea (Robberstad et al., 2004; Mejia et al., 2015; Shillcutt et al., 2017), these studies have been performed in the context of therapeutic zinc supplementation, and the outcomes for prophylactic zinc may differ. In addition, the few cost-effectiveness studies for prophylactic zinc have been conducted among children older than 6 months of age (Brown et al., 2013; Chhagan et al., 2013; Fink and Heitner, 2014) and none have been performed using data from East Africa. This study was therefore conducted to fill the knowledge gap with regards to the cost-effectiveness of prophylactic zinc supplementation in preventing various forms of diarrhoea in children aged between 6 weeks and 18 months in an east African setting. A decision-analytic model of zinc supplementation for young children in Tanzania was tested to determine the cost-effectiveness of prophylactic zinc supplementation.

Methods

Analytic approach

We investigated the incremental costs and benefits of preventive zinc supplementation using a model parameterized with local Tanzanian data on costs, diarrhoeal disease epidemiology, and effectiveness of zinc supplementation. The model was used to estimate costs and health outcomes for a hypothetical cohort of 10,000 children aged 6 weeks to 18 months under different scenarios. The incremental cost-effectiveness of preventive zinc supplementation was calculated as the difference in costs and health outcomes between a scenario with preventive zinc supplementation as compared to a scenario describing current standard-of-care (no supplementation).

Hypothetical zinc supplementation program

For the zinc supplementation program, we assumed that children up to 6 months of age would receive one 5 mg zinc capsule per day (250% of the Adequate Intake in this age group) (McDonald et al., 2015), and children 7 to 18 months of age would receive two 5 mg capsules per day (333% of the Recommended Dietary Allowance) (Institute of Medicine, 2001). It was assumed zinc supplementation would be delivered with the same approach as used in a zinc clinical trial in Tanzania (McDonald et al., 2015), where caregivers were instructed how to open the blister pack and the capsule, dilute the zinc powder in small cup with 5 ml sterile water, and feed the supplement to the child.
We assumed the supplementation intervention would be delivered through child clinics conducted routinely at health facilities, with zinc supplementation provided together with other routine clinical services (growth monitoring, vaccination, nutrition counselling and general health education). Tanzanian children are recommended to attend clinic monthly for growth monitoring up to 5 years of age (Ministry of Health, Community Development, Gender, 1980). In practice, attendance is high until 18 months of age (1.5 years) a time when most of the vaccination schedule has been completed (Tanzania Ministry of Health, 2016). The supplement would be distributed to caretakers at two contacts. The first distribution would occur at the 6 weeks visit, and dispense 8 months’ worth of zinc supplementation. The second distribution would occur at the 9 months visit, dispensing a subsequent 9 months’ worth of zinc supplementation. Instruction on dosage, timing, and how to prepare the supplement would be provided each time the supplement is provided to the caregiver.

**Effectiveness of zinc in preventing diarrhea**

The effectiveness of zinc in preventing diarrhea was established by a large clinical trial in Tanzania (McDonald et al. 2015). Information on rate ratios for diarrhoeal incidence was obtained from the trial (Table 1) and we estimated the incremental difference in diarrhoea incidence over a 17-month analytic period (up to 18 months of age). The number of diarrhoea episodes averted was estimated as the difference in diarrhoea episodes with zinc supplementation compared to diarrhoea episodes without zinc supplementation. Total diarrhoea episodes without zinc were calculated as a product of the annual incidence rate for diarrhoea, the analytic period in years, and cohort size. We calculated the total diarrhoea episodes with zinc supplementation by multiplying this total by the rate ratio associated with zinc supplementation. We assumed that adherence with the intervention in routine practice would be lower than observed in the trial setting (Rothwell, 2006), and that reductions in compliance would reduce health benefits proportionally (e.g. 80% compliance would reduce health benefits by 20% compared to compliance in the trial).

**Cost of zinc supplementation and care for diarrhoeal illness**

We estimated the average cost of zinc supplementation based on the raw materials cost (zinc and packaging). These costs were calculated as the daily cost of zinc multiplied by the number of days supplemented and number of children supplemented. As zinc would be delivered during routine clinic visits we assumed there would be no additional visits required to deliver the intervention. The costs associated with episodes of diarrhoeal illness were
calculated to determine cost-savings that may be realized from zinc supplementation. For each strategy (supplementation vs. no supplementation) we estimated the total cost of outpatient care as the product of the total number of diarrhoeal episodes, the number of clinic visits per episode, and the cost per clinic visit. We also estimated the costs of hospitalization associated with diarrheal care, calculated as the product of the total number of diarrhoeal episodes, the probability of hospitalizations per episode, the average duration of hospitalization, and the cost per-bed day for hospitalization. For both outpatient and hospital-based care, cost inputs included provider costs (medications and service provision), and costs borne by caregivers (out-of-pocket spending and productivity losses). Sources of cost data included secondary cost data from WHO-CHOICE (WHO, 2019) and similar studies (Robberstad et al., 2004; Tate et al., 2009; Brown et al., 2013; Fink and Heitner, 2014; Ruhago et al., 2015; WHO, 2019). Input values and sources are shown in Table 1.

Cost adjustment
We adjusted costs to be representative of 2019 Tanzanian price levels (Turner et al., 2019). For cost inputs obtained from other settings (Tate et al., 2009), we adjusted for price differences between settings using health sector price indices reported by the World Bank’s International Comparison Program (World Bank, 2020). To adjust for inflation, we first converted cost inputs into Tanzanian Shillings using exchange rates reported by the Bank of Tanzania for the years in which cost data were collected, then inflated costs to 2019 levels using the GDP deflator (The World Bank, 2020). We converted the resulting cost estimates to US dollars using the 2019 exchange rate (Bank of Tanzania, 2020). All results are reported in 2019 US dollars.

Disability adjusted life years averted by zinc supplementation
Disability adjusted life years (DALYs) averted were calculated to quantify health outcomes. DALY estimation considered Years of Life Lost (YLL) due to premature mortality and Years Lived with Disability (YLD) due to non-fatal health losses resulting from diarrhoea. YLLs were calculated as the product of the estimated number of diarrhoeal deaths (total diarrhoeal episodes multiplied by case fatality) and standard life expectancy at the age of diarrhoeal death (Global Burden of Disease Collaborative Network, 2021). To calculate YLDs we multiplied the number of person-years spent with diarrhoea (total diarrhoeal episodes multiplied by average disease duration) by the disability weight for mild diarrhoea (Salomon et al., 2015). To this we added the number of person-years spent hospitalized due to diarrhoea.
(number of diarrhoea hospitalizations multiplied by average duration of hospitalization) multiplied by the disability weight for severe diarrhoea. Parameter inputs for calculating DALYs were obtained from the zinc trial, published literature, and standard values used in the Global Burden of Disease study (Table 1). DALYs were discounted using a 3% discount rate (Wilkinson et al., 2016).

Cost-effectiveness of zinc supplementation

We estimated the incremental cost-effectiveness ratio (ICER) comparing zinc supplementation to the standard-of-care. The primary cost-effectiveness outcome was the incremental cost per DALY averted, with costs assessed from a societal perspective and a discount rate of 3% applied to future outcomes (Wilkinson et al., 2016). We also calculated the incremental cost per DALY averted from a health system perspective (omitting patient-incurred costs), and present both outcomes with and without discounting. We also report the cost per diarrhoea episode averted, from societal and health system perspectives, without discounting.

Uncertainty and sensitivity analysis

We conducted several sensitivity analyses to describe the robustness of model results to changes in model parameters (Briggs et al., 2012). Firstly, we conducted deterministic one-way sensitivity analyses for each model parameter. To do so, we varied each parameter between its upper and lower bounds (Table 1) while holding other parameters at their mean value, and recorded the resulting change in the primary ICER outcome. Secondly, we conducted a probabilistic sensitivity analysis to describe the combined impact of uncertainty in all model parameters. We specified closed-form prior distributions for each model parameter (beta distributions for probabilities and other parameters defined between zero and one, and gamma distributions for risk ratios and other non-negative parameters), with the mean and dispersion of these distributions chosen to reproduce the mean and interval widths for each parameter (Table 1). Using these distributions we drew a latin hypercube sample of 100,000 parameter sets and performed a 2nd-order Monte Carlo simulation. With the results produced we calculated equal-tailed 95% uncertainty intervals for each major outcome (Briggs et al., 2012). We also used these results to calculate cost-effectiveness acceptability curves (Fenwick, Claxton and Sculpher, 2001), describing the probability that zinc supplementation is cost-effective for different threshold values for the cost per DALY averted.
To draw conclusions about cost-effectiveness we compared ICERs and cost-effectiveness acceptability curves to conventional cost-effectiveness thresholds, with a cost-effectiveness ratio below the threshold indicating that is cost-effective. The thresholds included 1 times and 3 times per capita GDP, which have been proposed by the Commission on Macroeconomics and Health (WHO Commission on Macroeconomics and Health, 2001) and subsequently adopted by WHO-CHOICE for resource allocation decisions (Hutubessy, Chisholm and Tan-Torres Edejer, 2003), as well as more recently published thresholds that attempt to quantify the opportunity costs of reallocating spending within the health budget (Woods et al., 2016; Ochalek, Lomas and Claxton, 2018). These recent thresholds produce more stringent criteria for identifying an intervention as cost-effective.

In addition, we examined how results changed when we used estimates from a recent meta-analysis to parameterize the effect of zinc supplementation (Keats et al., 2021), instead of the estimates reported by McDonald et al. (2015). In this meta-analysis, prophylactic zinc was found to reduce diarrhoea incidence with a rate ratio of 0.89 (95% CI 0.82–0.97) and reduce the average duration of diarrheal episodes by 0.5 days.

**Results**

**Cost of zinc supplementation**

Zinc supplementation was estimated to cost $109,800 (95% uncertainty interval (95%UI): 61,716–171,507) for the study cohort of 10,000, equivalent to $11 per child. The provider cost of diarrhoea treatment (outpatient and hospitalization) was estimated to be $78,347 (95%UI: 42,694–136,095) without zinc supplementation and $70,734 (95%UI: 38,286–123,212) with zinc supplementation, equivalent to cost savings of $7,613 (95%UI: 2,295–15,878) with zinc supplementation, or $0.76 per child. The cost incurred by patients in their families for diarrhoea treatment (outpatient and hospitalization), which includes out-of-pocket spending and lost productivity, was estimated to be $66,312 (95%UI: 39,875–103,535) without zinc supplementation and $59,868 (95%UI: 35,728–93,837) with zinc supplementation, equivalent to cost savings of $6,444 (95%UI: 2,045–12,529) with zinc supplementation, or $0.64 per child. Combining patient and health services costs, total cost-savings from averted diarrhoea care were $12,887 (95%UI: 4,089–25,058). Additional cost outcomes are described in Table 2.
Effectiveness of zinc supplementation

Zinc supplementation was estimated to avert 2,200 (95%UI: 776–3,737) episodes of diarrhoea, 1,584 (95%UI: 522–2,927) outpatient visits, 561 (95%UI: 160–1,189) hospital bed-days, 0.51 (95%UI: 0.15–1.03) deaths, and 14,080 (95%UI: 4,692–25,839) sick days. Taken together, this resulted in 3.2 (95%UI: 1.0–6.3) fewer YLDs, and 43.5 (95%UI: 12.9–87.6) fewer YLLs. Detailed health outcomes for each strategy are reported in Table 2. In aggregate, we estimated 46.7 (95%UI: 14.3–92.6) fewer DALYs for the zinc supplementation strategy compared to no supplementation (equivalent to 19.3 (95%UI: 6.1–37.5) discounted DALYs) (Table 3).

Incremental cost-effectiveness ratios for zinc supplementation

For the primary cost-effectiveness outcome (societal perspective, 3% discount rate applied to future outcomes) the ICER of zinc supplementation was $4,950 (95%UI: 1,678–17,933) per DALY averted, as compared to no supplementation. Without discounting the ICER was substantially lower, $2,049 (95%UI: 686–7,624) per DALY averted, reflecting the time lag between intervention spending and the life-years gained through reduced diarrhoeal mortality. ICERs estimated from a health system perspective were similar to the results from the societal perspective (Table 3). The incremental cost per diarrhoeal episode averted was $57 (95%UI: 19–145) from a societal perspective, and $54 (95%UI: 16–142) from a health system perspective. Figure 1 shows the probability that zinc supplementation is cost-effective compared to no supplementation, for different values of the cost-effectiveness threshold, with and without discounting, and compared to different criteria for identifying an intervention as cost-effective.

Sensitivity analyses

We conducted deterministic one-way sensitivity analyses for each model parameter. Figure 2 summarizes these results for the ten most influential parameters. Of these parameters, uncertainty in the risk ratio of diarrhoea with zinc supplementation had the greatest impact on the cost-effectiveness results, with the cost per DALY averted rising from $2,857 to $16,289 as this parameter was varied from its lowest to highest value. The unit cost of zinc supplementation was also influential, with the cost per DALY averted rising from $2,157 to $7,832 as this parameter was varied from its lowest to highest value.
When we re-ran the analysis using input data from Keats et al. (2021) we found very similar results compared to the main analysis, with a cost per DALY averted of $4,890 (95%UI: 1,715–16,328) for the primary cost-effectiveness outcome, 1% lower than the ICER estimated in the main analysis.

**Discussion**

In this study, prophylactic zinc supplementation for infants and children in Tanzania was shown to reduce the health losses, health care utilization, and productivity losses associated with childhood diarrhoea. This included averting episodes of diarrhoea, reducing outpatient visits and inpatient days for diarrhoea, reducing sick days, and reducing diarrhoeal deaths in the study population. These results are consistent with other studies that have estimated the benefits of zinc supplementation for therapy as well as prevention. For example, recent clinical trials conducted in Tanzania have shown that daily zinc supplementation for infants can reduce the burden of diarrhoea (McDonald *et al.*, 2015; Dhingra *et al.*, 2020). Other similar studies have reported reduced episodes of diarrhoea (Bhutta *et al.*, 1999; Aggarwal, Sentz and Miller, 2007; Yakoob *et al.*, 2011), reduced duration of diarrhoea (Aggarwal, Sentz and Miller, 2007; Gregorio *et al.*, 2007; Lazzerini and Wanzira, 2016), reduced severity of diarrhoea (Aggarwal, Sentz and Miller, 2007), reduced diarrhoea mortality (Yakoob *et al.*, 2011; Penny, 2013), and reduced mean cost of diarrhoea treatment (Gregorio *et al.*, 2007).

However, our results also show relatively high costs for implementing prophylactic zinc supplementation. The mean cost of supplementation was $11 per child. Other studies have reported high cost of zinc supplementation as well (Patel, Badhoniya and Dibley, 2013). Driven by these high implementation costs, our results demonstrate that prophylactic zinc supplementation may not be cost-effective for the prevention of childhood diarrhoea in settings like Tanzania. While there is considerable uncertainty about the appropriate cost-effectiveness threshold to apply in low- and middle-income countries, most conventional estimates suggest that interventions should have a cost per DALY averted that is substantially below a country’s per-capita GDP to be considered cost-effective (Woods *et al.*, 2016; Ochalek, Lomas and Claxton, 2018). The primary cost-effective ratio estimated in this study—$4,950 per DALY averted—is well above the per-capita GDP in Tanzania (US$1,122 in 2019 (World Bank, 2021)), suggesting that the health and economic benefits produced by reduced diarrhoea incidence do not justify the costs required to implement the intervention. Even with more relaxed thresholds of 1 times and 3 times per capita GDP—now thought to
be a poor representation of the opportunity cost of healthcare spending in settings like Tanzania (Marseille et al., 2015)—supplementation does not appear cost-effective.

In sensitivity analysis we found that this cost-effectiveness ratio was most sensitive to the unit costs of supplementation, as well as the risk ratio for the reduction in diarrheal risk with supplementation. As a consequence, this intervention could become cost-effective if there were price reductions for the zinc tablets, or if accumulating evidence suggested greater risk reductions for supplementation. There are good reasons to believe that lower intervention costs are possible. Firstly, the cost of zinc supplementation could go down in light of the findings from a recent large clinical trial carried out among children in Tanzania and India, which found that lower doses of zinc (5mg and 10mg) were non-inferior with respect to duration of diarrhoea and number of stools during an episode, compared to the WHO recommended 20mg dose (Dhingra et al., 2020).

Despite the lack of cost-effectiveness of the zinc supplementation scenario presented in our modelling findings, many studies have suggested zinc supplementation may be of benefit in high diarrhoea burden areas where childhood zinc deficiency and malnutrition is prevalent (Penny, 2013; Lazzerini and Wanzira, 2016). It is possible that an intervention with a more favourable cost-effectiveness ratio could be achieved by targeting prophylactic zinc supplementation to lower income households with a high burden of childhood malnutrition and diarrhoea.

A major strength of this study was the availability of local data required for the analysis. This allowed us to parameterize the study model with evidence collected in the setting of interest, including the clinical trial that estimated the risk ratio of diarrheal incidence attributable to zinc supplementation (Mcdonald et al., 2015). Another strength of the study is that it responds to a clear gap in the evidence base for zinc supplementation, as there are very few studies on the cost-effectiveness of prophylactic zinc supplementation (Brown et al., 2013). Moreover, cost-effectiveness studies on therapeutic zinc have reported inconsistent results, with some reporting cost-effectiveness of zinc in treating childhood diarrhoea (Gregorio et al., 2007; Brown et al., 2013), while other report no cost-effectiveness (Patel, Badhoniya and Dibley, 2013).

This study also has several limitations. First, the major outcomes (changes in DALYs and diarrheal mortality) were not estimated empirically, but instead relied on decision-analytic modelling to extrapolate outcomes, based on expected differences in diarrheal incidence.
While modelling plays an important role in generalizing the results of empirical trials, the construction of models requires additional assumptions. In this study major assumptions were the base rate of diarrheal illness, and the case fatality associated with diarrheal illness. For this reason, further empirical assessment of the cost and health impacts of prophylactic zinc supplementation would add robustness to the findings of this study. Secondly, we did not model the potential health benefits of prophylactic zinc on pneumonia incidence. The evidence base supporting preventive effects for pneumonia is relatively weak, with Keats et al. (2021) reporting a risk ratio of 0.87 (95% CI 0.81–0.94) for pneumonia incidence, with a low GRADE assessment. However, if prophylactic zinc does prevent pneumonia this could substantially improve cost effectiveness, as pneumonia causes many more under-5 deaths and DALYs in Tanzania than diarrhoea (Institute for Health Metrics and Evaluation-Global Burden of Disease Collaborative Network, 2021). For this reason, our cost-effectiveness results should be revisited if evidence confirms a protective effect for zinc supplementation against pneumonia. Thirdly, although the Tanzanian zinc supplementation trial reported a statistically significant reduction in diarrhoea incidence, there were no statistically significant differences observed for outpatient visits, hospitalizations, and mortality (McDonald et al., 2015). In contrast, our modelling allowed for reductions in these outcomes proportional to the effect on diarrhoea incidence. As these other outcomes have a lower base rate in the study cohort, it is not surprising that statistically non-significant differences were reported for these outcomes, due to the relatively modest rate ratio for diarrhoea (0.78) reported by the study. However, if zinc supplementation truly has no effect on these outcomes it would make zinc supplementation substantially less cost-effective. Fourthly, it is possible that the analysis did not sufficiently adjust for the lower level of compliance in routine settings compared to the trial. In the analysis we assumed compliance would be 81% (70, 90) (Etheredge et al., 2015; Sambili et al., 2016). If compliance were to be substantially lower than this the cost-effectiveness of zinc supplementation would be worse, as intervention costs would be unchanged but health benefits proportionally lower.

Conclusion
Prophylactic zinc has positive health and economic benefits; however it was not found to be cost-effective for prevention of childhood diarrhoea in the scenarios examined in this study. Additional research is needed to identify intervention approaches that can achieve the health benefits of prophylactic zinc supplementation at lower implementation costs.
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**Figure 1: Cost-effectiveness acceptability curve for zinc supplementation versus no supplementation.**

Figure 2: Results of one-way sensitivity analyses*

* Incremental cost-effectiveness ratio (societal perspective, discounted at 3%).
### Table 1: Parameter estimates used in the model

<table>
<thead>
<tr>
<th>Category</th>
<th>Parameter description</th>
<th>Parameter value (95% uncertainty interval)</th>
<th>Distribution used for probabilistic sensitivity analysis</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort</strong></td>
<td>Cohort size</td>
<td>10000</td>
<td>Fixed value</td>
<td>Assumed zinc distributed to 10,000 children &gt; 6 weeks to 18 months old</td>
</tr>
<tr>
<td><strong>Risk of diarrhoea and sequelae</strong></td>
<td>Rate of diarrhoea episodes (per year)</td>
<td>1.530 (1.243, 1.844)</td>
<td>Gamma(99.4, 65.0)</td>
<td>(Global Burden of Disease Collaborative Network., 2020)</td>
</tr>
<tr>
<td></td>
<td>Average duration of diarrhoea, per episode (days)</td>
<td>6.4 (4.3, 8.4)</td>
<td>Gamma(37.3, 5.8)</td>
<td>(Lamberti, Fischer Walker and Black, 2012)</td>
</tr>
<tr>
<td></td>
<td>No. outpatient visits per episode, diarrhoea</td>
<td>0.72 (0.30, 0.78)</td>
<td>Gamma(34.4, 47.8)</td>
<td>(Sigei et al., 2015)</td>
</tr>
<tr>
<td>Probability of hospitalization with diarrhoea, per episode</td>
<td>0.064 (0.027, 0.069)</td>
<td>Beta(32.2, 472.3)</td>
<td></td>
<td>(McDonald et al., 2015; Sigei et al., 2015)</td>
</tr>
<tr>
<td>Average number of bed-days, per hospitalization</td>
<td>4.0 (2.0, 6.0)</td>
<td>Gamma(15.2, 3.8))</td>
<td></td>
<td>(Atherly et al., 2009; Ruhago et al., 2015)</td>
</tr>
<tr>
<td>Case fatality for diarrhoea</td>
<td>0.000232 (0.000142, 0.000379)</td>
<td>Beta(14.5, 62686)</td>
<td></td>
<td>Ratio of diarrheal mortality to diarrheal incidence in individuals Under 5 years of age(Global Burden of Disease Collaborative Network., 2020)</td>
</tr>
<tr>
<td>Intervention parameter</td>
<td>Risk ratio of diarrhoea with zinc supplementation</td>
<td>Gamma(528.7, 600.8)</td>
<td>(McDonald et al., 2015)</td>
<td></td>
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<tr>
<td>Compliance with zinc supplementation (%)</td>
<td>81</td>
<td>Beta(46.4, 10.9)</td>
<td>(Etheredge et al., 2015; Sambili et al., 2016)</td>
<td></td>
</tr>
<tr>
<td>Number of units of zinc dispensed</td>
<td>540</td>
<td>Fixed value</td>
<td>Total months multiplied by 30 days per month</td>
<td></td>
</tr>
<tr>
<td>Unit costs*</td>
<td>Unit cost of an outpatient visit (service provision, US$)</td>
<td>1.05</td>
<td>Gamma(1.6, 1.5)</td>
<td>(WHO, 2019)</td>
</tr>
<tr>
<td></td>
<td>Unit cost of an outpatient visit (medication and diagnostics, US$)</td>
<td>1.63</td>
<td>Gamma(60.5, 37.1)</td>
<td>(Tate et al., 2009)</td>
</tr>
<tr>
<td></td>
<td>Unit cost of an outpatient visit (caregiver lost productivity, US$)</td>
<td>1.47</td>
<td>Gamma(6.7, 4.5)</td>
<td>(Tate et al., 2009)</td>
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<tr>
<td></td>
<td>Unit cost of an outpatient visit (caregiver out-of-pocket costs, US$)</td>
<td>0.88</td>
<td>Gamma(4.4, 5.0)</td>
<td>(Tate et al., 2009)</td>
</tr>
<tr>
<td></td>
<td>Unit cost of a hospital bed-day (service provision, US$)</td>
<td>4.79</td>
<td>Gamma(4.7, 1.0)</td>
<td>(WHO, 2019)</td>
</tr>
<tr>
<td></td>
<td>Unit cost of hospitalization (medication and diagnostics, US$)</td>
<td>4.86</td>
<td>Gamma(61.3, 12.6)</td>
<td>(Tate et al., 2009)</td>
</tr>
<tr>
<td>Other inputs</td>
<td>Description</td>
<td>Value</td>
<td>Distribution</td>
<td>Reference</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>-----------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Unit cost of hospitalization (caregiver lost productivity, US$)</td>
<td>6.45 (2.49, 10.47)</td>
<td>Gamma(9.9, 1.5)</td>
<td>(Tate et al., 2009)</td>
</tr>
<tr>
<td></td>
<td>Unit cost of hospitalization (caregiver out-of-pocket costs, US$)</td>
<td>12.95 (8.93, 16.91)</td>
<td>Gamma(40.3, 3.1)</td>
<td>(Tate et al., 2009)</td>
</tr>
<tr>
<td></td>
<td>Unit cost of zinc supplementation (30 days supply, US$)</td>
<td>0.61 (0.31, 0.92)</td>
<td>Gamma(15.2, 24.9)</td>
<td>(Brown et al., 2013; Fink and Heitner, 2014; Medical Stores Department, 2018)</td>
</tr>
<tr>
<td></td>
<td>Years of Life Lost (YLL) per death in target population</td>
<td>85.21</td>
<td>Fixed value</td>
<td>(Global Burden of Disease Collaborative Network, 2021)</td>
</tr>
<tr>
<td></td>
<td>Disability weight for diarrhoea, mild</td>
<td>0.074 (0.049, 0.104)</td>
<td>Gamma(27.6, 373.5)</td>
<td>(Salomon et al., 2015)</td>
</tr>
<tr>
<td></td>
<td>Disability weight for diarrhoea, severe</td>
<td>0.247 (0.164, 0.348)</td>
<td>Gamma(27.5, 111.4)</td>
<td>(Salomon et al., 2015)</td>
</tr>
<tr>
<td></td>
<td>Discount rate</td>
<td>3%</td>
<td>Fixed value</td>
<td>(Wilkinson et al., 2016)</td>
</tr>
</tbody>
</table>

* All costs reported in 2019 US dollars.
Table 2: Outcomes and costs for standard-of-care and zinc supplementation strategies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard-of-care</th>
<th>Zinc supplementation</th>
<th>Incremental difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of diarrheal episodes</td>
<td>22636 ( (18406, 27297) )</td>
<td>20435 ( (16426, 24911) )</td>
<td>-2200 ( (-3737, -776) )</td>
</tr>
<tr>
<td>Number of outpatient visits for diarrhea</td>
<td>16297 ( (10704, 23319) )</td>
<td>14713 ( (9598, 21178) )</td>
<td>-1584 ( (-2927, -522) )</td>
</tr>
<tr>
<td>Number of hospitalizations for diarrhea</td>
<td>1444 ( (946, 2065) )</td>
<td>1304 ( (848, 1878) )</td>
<td>-140 ( (-259, -47) )</td>
</tr>
<tr>
<td>Number of hospital bed-days for diarrhea</td>
<td>5775 ( (2808, 10152) )</td>
<td>5214 ( (2526, 9227) )</td>
<td>-561 ( (-1189, -160) )</td>
</tr>
<tr>
<td>Number of deaths from diarrhoea</td>
<td>5.251 ( (2.788, 8.569) )</td>
<td>4.741 ( (2.509, 7.769) )</td>
<td>-0.510 ( (-1.029, -0.152) )</td>
</tr>
<tr>
<td>Number of days with diarrhoea</td>
<td>144866 ( (96555, 205331) )</td>
<td>130786 ( (86570, 186518) )</td>
<td>-14080 ( (-25839, -4692) )</td>
</tr>
<tr>
<td>YLDs due to diarrhoea</td>
<td>33.3 ( (19.8, 52.2) )</td>
<td>30.0 ( (17.8, 47.3) )</td>
<td>-3.2 ( (-6.3, -1.0) )</td>
</tr>
<tr>
<td>YLLs due to diarrhoea</td>
<td>447.5 ( (237.6, 730.2) )</td>
<td>404.0 ( (213.7, 662.0) )</td>
<td>-43.5 ( (-87.6, -12.9) )</td>
</tr>
<tr>
<td>YLLs due to diarrhoea, discounted at 3%</td>
<td>165.8 ( (88.0, 270.5) )</td>
<td>149.7 ( (79.2, 245.2) )</td>
<td>-16.1 ( (-32.5, -4.8) )</td>
</tr>
<tr>
<td>Health system costs of outpatient diarrhoea care</td>
<td>43671 ( (21569, 85433) )</td>
<td>39428 ( (19401, 77295) )</td>
<td>-4243 ( (-9627, -1203) )</td>
</tr>
<tr>
<td>Patient costs of outpatient diarrhoea care</td>
<td>38295 ( (16831, 71040) )</td>
<td>34574 ( (15155, 64368) )</td>
<td>-3721 ( (-8224, -991) )</td>
</tr>
<tr>
<td>Health system costs of hospitalization for diarrhoea</td>
<td>34676 ( (12857, 76823) )</td>
<td>31306 ( (11574, 69398) )</td>
<td>-3370 ( (-8504, -795) )</td>
</tr>
<tr>
<td>Patient costs of hospitalization for diarrhoea</td>
<td>28018 ( (16459, 43843) )</td>
<td>25295 ( (14774, 39822) )</td>
<td>-2723 ( (-5312, -857) )</td>
</tr>
<tr>
<td>Cost of zinc supplement</td>
<td>0 ( (0, 0) )</td>
<td>109,800 ( (61716, 171507) )</td>
<td>109,800 ( (61716, 171507) )</td>
</tr>
</tbody>
</table>

* Calculated as zinc supplementation minus base-case. All costs reported in 2019 US dollars.
Table 3: Cost-effectiveness results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Base case</th>
<th>Zinc supplementation</th>
<th>Incremental difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DALYs due to diarrhoea</td>
<td>480.7 (268.4, 767.8)</td>
<td>434.0 (241.8, 694.2)</td>
<td>-46.7 (-92.6, -14.3)</td>
</tr>
<tr>
<td>DALYs due to diarrhoea, discounted at 3%</td>
<td>199.0 (117.9, 307.9)</td>
<td>179.7 (106.1, 279.0)</td>
<td>-19.3 (-37.5, -6.1)</td>
</tr>
<tr>
<td>Total costs (health system perspective)</td>
<td>78347 (42694, 136095)</td>
<td>180534 (118790, 258104)</td>
<td>102187 (53410, 164354)</td>
</tr>
<tr>
<td>Total costs (societal perspective)</td>
<td>144659 (91185, 220646)</td>
<td>240403 (168001, 329811)</td>
<td>95744 (46209, 158172)</td>
</tr>
<tr>
<td>ICER (health system perspective, undiscounted)</td>
<td>---</td>
<td>---</td>
<td>2187 (806, 7808)</td>
</tr>
<tr>
<td>ICER (societal perspective, undiscounted)</td>
<td>---</td>
<td>---</td>
<td>2049 (686, 7624)</td>
</tr>
<tr>
<td>ICER (health system perspective, discounted)</td>
<td>---</td>
<td>---</td>
<td>5283 (1976, 18335)</td>
</tr>
<tr>
<td>ICER (societal perspective, discounted)</td>
<td>---</td>
<td>---</td>
<td>4950 (1678, 17933)</td>
</tr>
</tbody>
</table>

* Calculated as zinc supplementation minus base-case. All costs reported in 2019 US dollars.