Water treatment and child mortality: a systematic review and meta-analysis

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Summary

Background

Randomized controlled trials (RCTs) of water treatment are typically powered to detect effects on caregiver-reported diarrhea but not child mortality, as detecting mortality effects requires prohibitively large sample sizes. To increase statistical power, we conducted a meta-analysis that combined available RCT evidence on child mortality with new evidence on mortality obtained from authors of studies reporting only diarrhea outcomes.

Methods

We first identified studies published between 1970 and February 2016 that examined the impact of water quality interventions on diarrhea in low- or middle- income countries and were identified by previous meta-analyses. Next, the same selection criteria and search procedure as followed in (50) were replicated to add more recent studies (last search was conducted on April 20, 2020). Included studies were restricted to randomized controlled trials (RCTs) of interventions to improve microbiological water quality in low- or middle-income countries (according to the World Bank classification) which included children less than five years of age. We then obtained child mortality (under 5 years old) data from each study for which it was collected. We included 15 studies in our analysis whose characteristics are outlined in Table 1. The Newcastle-Ottawa scale was used to assess risk-of-bias for all selected studies. Frequentist and Bayesian methods were then used to estimate the effect of water treatment on child mortality among included studies. Meta-analysis results were then combined with cost data to estimate

cost-effectiveness in the context of (1) a point-of-collection chlorine dispenser program in Western Kenya and (2) a large-scale program providing coupons for free chlorine solution.

Findings

We identified 52 RCTs of water quality interventions and included 15 RCTs that had data on child mortality in this meta-analysis. The resulting meta-analysis of the full sample estimated a mean (cross-study) reduction in the odds of all-cause child mortality of about 30% (Peto odds ratio, OR, 0.72; 95% CI 0.55 to 0.92; Bayes OR 0.70; 95% CrI 0.49 to 0.92). The I-squared was 6% in the Bayesian model and 29% in the Peto OR specification and we cannot reject the hypothesis of homogeneous effects (p-value = 0.14).

We estimate a cost per DALY averted due to water treatment of USD 36 for chlorine dispensers in Western Kenya and USD 34 for a hypothetical large-scale coupon program.

Interpretation

A meta-analysis combining RCT evidence on child mortality, identified using a systematic literature search, together with new RCT evidence obtained from authors of studies that reported only diarrhea outcomes, implies that water treatment reduces the odds of all-cause child mortality by about 30%.

Taking cost data from two water treatment interventions in Kenya and Malawi, the estimated number of DALYs averted per dollar is more than fifty times greater than the WHO's cost threshold for "highly cost-effective" interventions.

The estimated effect in the meta-analysis is larger than would be estimated by a simple model that assumes that diarrheal deaths are linear in diarrhea cases and takes total diarrheal death from global burden of disease estimates and reductions in diarrhea due to water treatment from (35). Differences could be accounted for by known epidemiological factors not captured by this simple linear model and uncertainty in parameters.

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Introduction

Each year over two billion people consume drinking water contaminated with feces (1) and over 1.5 million people die from diarrheal diseases (2). Climate change and aquifer depletion threaten existing sources of clean water (3). Yet relatively basic measures to contain disease spread from fecally-contaminated water remain unimplemented in large parts of the world. Chlorination, for example, has been found to be effective in reducing the concentration of diarrheal pathogens like *E.coli* in controlled laboratory settings (4-7) and reducing caregiver-reporter diarrhea (8, 9), and a variety of low-cost delivery systems exist, in addition to municipal water systems. However, in low-income countries, only 28% of the population have access to safely managed drinking water facilities (10).

Water treatment is often not included in lists of cost-effective, evidence-backed child survival interventions which are recommended for prioritization in health funding decisions, and health funds are typically not used to cover the cost of water treatment at scale. This may in part be due to a lack of RCT evidence on the effect of water treatment on child mortality. Conducting adequately powered randomized controlled trials (RCTs) to measure the impact of water treatment on child mortality requires very large sample sizes and correspondingly large costs. Therefore, RCTs measuring the impact of water treatment are typically powered to detect effects on the intermediate outcome of caregiver-reported child diarrhea rather than child mortality. However, caregiver reports of child diarrhea may be subject to reporting bias (11, 12). Some have therefore recommended the need for studies which are either blinded or include as a primary outcome an objective outcome such as mortality (11).

To increase statistical power to detect child mortality impacts, we conducted a literature search aimed at combining existing RCT evidence on mortality with new evidence we obtained from authors of studies reporting other outcomes. We then used a meta-analysis to estimate the impact and cost-effectiveness of water quality interventions on child mortality.

Methods

This systematic review was registered within the AEA under the registration number AEARCTR-0005977, and can be accessed here https://www.socialscienceregistry.org/trials/5977.

We followed PRISMA 2020 guidelines (13); Table S10 and S11 provides an overview.

Search strategy and selection criteria

The first step was a review of all studies identified by previous meta-analyses (8, 9) of studies from 1970 to February 2016 examining the impact of water quality interventions on diarrhea. Next, the search procedure and selection criteria followed by a previous meta-analysis (9) were replicated for the period from February 2016 to May 2020 to add more recent studies (last date search was conducted is April 20, 2020). The selection criteria was updated to allow for manuscripts published during the eligibility period that were updated after the period concluded. As detailed in Table S1, the search included Pubmed, Embase, Scopus and Cochrane Library using both keywords and MeSH terms to identify all studies of interventions to improve water quality. Additional papers for review were also included based on reference sections of all papers, as well as recommendations from subject matter experts.

Included studies were restricted to randomized controlled trials (RCTs) of interventions to improve water quality (in the microbiological sense) in low- or middle-income countries (according to the World Bank classification) which included children less than five years of age. The choice of including only RCTs was made to focus on studies that can estimate causal impacts with minimal methodological assumptions.

Data extraction and quality assessment

Study title and abstract screening, filtering studies in accordance with the inclusion criteria, data extraction, and quality assessment were independently performed by two reviewers. Both author-provided and publicly available individual-level data on child (<5 years) mortality were used for the study. Data were collected through surveys, and all available data on mortality were considered.

We also extracted summary data on all studies in (9), to compare key characteristics between studies included in this meta-analysis and excluded studies (Materials and methods, section 4). These data were extracted from the appendix section of (9).

Two review authors independently assessed the risk of bias using the Newcastle-Ottawa scale (14), as used in (9). For each study included in this review, we used information provided in the study to evaluate the risk of bias coming from sample selection, responses bias (blinding versus

no-blinding), treatment allocation, follow-up bias (attrition), degree of treatment exposure, compliance, the dimension of the assessment, and measurement of the outcome.

Data analysis

For the meta-analysis we used an odds ratio (OR) outcome with random effects. To calculate ORs we used mortality counts extracted from publications or individual-level data. From a biological viewpoint, the choice of OR seems more appropriate than modeling risk difference (RD) and, when events are rare (as is the case with child mortality), the odds ratio approaches the risk ratio (RR) and therefore we did not compare OR and RR models. Moreover, the RD model is not appropriate when differences in mortality risk across studies is very large, as is the case in our sample, due to heterogeneity in length of follow-up, which we will discuss later. Therefore we included the RD model as a sensitivity analysis only. Since death is rare (typically 1-2% annualized risk), we chose models that are appropriate for estimating treatment effects for rare events. We fit both a frequentist Peto odds model and a Bayesian logistic model (15, 16). In both cases we chose a random effects model as our main specification due to heterogeneity in types of water quality interventions and study settings. The models are described in Materials and Methods, section 1. In future work, we hope to explore hazard rate models.

We focused on two samples of studies: all interventions and a sub-sample of studies that included water chlorination only. When existent, multiple treatment or control arms were combined so as to maximize power and to avoid introducing the correlation between treatment effect estimators that would arise if different treatments were compared to the same control group. For two studies (17, 18) which report the impact of closely related interventions on different samples, we report sensitivity to combining these studies. For 13 out of 15 studies, water treatment was compared to a pure control group which received no intervention. In two of these, several experimental arms were combined. These included some combination of water chlorination, flocculant-disinfection, and safe storage vessels (19, 20). In two cases, water treatment was combined with another intervention, cookstoves (21) or other sanitation and hygiene interventions (22).

We conducted sensitivity analyses to understand how researcher choices on data inclusion and modeling assumptions could impact the meta-analysis estimates. Additional detail explaining these analyses case-by-case, as well as detailed results, are given in Materials and Methods, section 2. To understand the impact of model choice, we fitted: (i) a fixed effects (Bayesian logit) model instead of random effects, (ii) an inverse variance model instead of Peto OR model, and (iii) a risk difference model instead of OR.

For sensitivity to choice of data, we considered the following: (i) exclusion of any particular study from the analysis, (ii) combining two studies that measure impacts of a similar program on different populations (23, 18), (iii) the inclusion of studies with contaminated control groups (22, 52), (iv) the use of an alternative control group in a study with active and passive control arms (27), (v) use of an alternative treatment group in a spring protection study (24), (vi) restricting to studies with long monitoring durations, and (vii) dropping studies where water treatment was combined with another intervention (23, 20).

Possible publication bias was examined with the inspection of funnel plots and the use of Begg's and Andrews and Kasy's tests (29). We also estimate a publication bias adjusted OR estimate following Andrews and Kasy. We test for heterogeneity in treatment effect using a Peto OR meta-regression model, one covariate at a time.

All analyses and visualizations were performed with R, version 4.1.0.

Results

Systematic review

Figure 1 illustrates the search and the selection process. The search strategy identified 1485 studies: 1412 studies through databases and 73 studies included in (9) and (8). We screened these titles and abstracts to obtain a sample of 82 studies for full-text review. 52 studies matched the inclusion criteria and we requested child mortality from the authors of each study. Twenty five authors reported that they did not collect mortality data or that the data was no longer available. The author of one study died and the authors of nine studies did not reply. Excluded studies are given in Table S2.

The sample of 17 studies with mortality data is summarized in Table 1, based on information from manuscripts, aggregation of microdata, and correspondence with authors. Two of them were excluded from the main analysis due to contamination in the control group. In the blinded filtration study (25) the placebo filter removed more than 90% of the source water bacterial contaminant. Participants in the solar disinfection trial (26) were temporarily displaced due to political violence and following the displacement, most gathered water from standpipes with treated water—largely reducing the likelihood of source water contamination. Moreover, displacement could have affected adherence to solar disinfection practices. We report meta-analysis estimates including these two studies in a sensitivity analysis.

Publication bias

Neither Begg's or Andrews and Kasy's tests provided evidence of publication bias (see Figure S3 and Table S8) (27). An adjusted estimate of the OR obtained using Andrews and Kasy method was OR = 0.83 (CI 95% 0.74, 0.92). Since the power of these tests may be limited when applied to our sample of 15 studies, we also consider a post hoc simulation-based exploration of small-study bias; see Discussion.

Risk of bias assessment

Among the included studies, we assessed the bias attributed to the selection of studies as low. First, all included studies are randomized controlled trials. Second, although in only one out of the fifteen studies the participants were blinded, reporting bias or experimenter effects are unlikely (see Supplementary Material: Risk of Bias table). The mortality status of a child who was alive at baseline can be easily verified and is far less likely to be subject to reporting bias than caregiver-reported diarrhea outcomes based on recall.

In the sample of the included studies, six studies had Steve Luby as an author, two had Michael Kremer as an author, and one of these had Ricardo Maertens and Brandon Tan as an author. None of the authors have any financial interest in these results.

Characteristics of included studies

The 15 studies in the main specification included 25,256 participants. Twelve examined water chlorination, two examined water filtration, and one examined spring protection. In aggregate, 170 deaths occurred among 11,701 children in treatment arms (1.5%); in the control arms, 339 among 13,555 (2.6%). The annual risk of mortality in the pooled control group was about 1.7%. Intervention and participation characteristics of included studies.

The median follow-up length for mortality was 52 weeks, with the longest follow-up being 4-6 years (18). 13 studies were conducted in middle income countries, and two were conducted in low-income countries, according to the World Bank classification (28). The age at which children were enrolled, as well as the periods for which they were followed, varied across studies. Three studies (29, 23, 30) did not collect data for older children (>2 years) and one (30) study did not collect data on younger children (< 6 months).

Out of the 15 studies, 13 were conducted in rural areas, one was conducted in both rural and urban areas, and one was conducted in a peri-urban setting. The compliance rate in the sample ranged from a low of 27% to a high of 87%, with a median of 69%.

In all included studies, the primary outcomes were intermediate outcomes such as diarrhea, while mortality data was collected as a secondary outcome, as part of internal respondent tracking systems, or for IRB reporting purposes by the authors. Only five studies explicitly report mortality outcomes in the published manuscript, highlighting the importance of following up with authors to request the mortality data.

Baseline contamination levels of water in studies are also reported in Table 1. Contamination level measures are not consistently reported across studies. Four studies report 54 to 181 TTC/100 ml (thermotolerant coliforms, which include *E. Coli* and three other bacteria species). Another 4 studies report *E.Coli* concentration from 34 to 63 per 100 ml.

Estimates of diarrhea prevalence among the 15 included studies are representative of prevalence in low- and middle-income countries. Household surveys across 94 low- and middle-income countries found diarrhea prevalence in 2017 ranging from 3.2% to 66.4% across sub national units, with a median of 19.2% (31). Diarrhea prevalence rates (at baseline or, if baseline not available, in the control group) in our sample of studies range from 5.2% to 27.1%, with a population-weighted mean of 15.9%; this corresponds to the 36th percentile of the distribution of sub national diarrhea estimates (see Figure 2).

We also provide comparisons of key characteristics of the water treatment studies included with those excluded from the analysis, but included in (9), and find them to be similar (Materials and Methods, section 4).

Meta-analysis

In the full set of 15 studies we estimated an average reduction in odds of all-cause child mortality of 28% (Peto OR 0.72; CI 95% 0.55, 0.92) or 30% (Bayes OR 0.70; CrI 95% 0.49, 0.92), depending on the model (see Figure 2, Table S3). Restricting the analysis to studies including chlorination, the reduction was 31% (Peto OR 0.69; CI 95% 0.47, 1.01) or 32% (Bayes OR 0.68; CrI 95% 0.37, 1.02).

Sensitivity to choice of data: For all sensitivity analyses of data choices that we performed (Materials and Methods, section 2), the study estimates remained qualitatively similar to our main estimate, with mean OR estimates ranging from 0.65 to 0.81. All credible/confidence intervals were below 1.

Sensitivity to choice of model: under a fixed effect Bayesian logit model the reduction in odds was 25% (OR 0.75, 95% CrI 0.61, 0.91), compared to 30% under the random effects model. Using the inverse weighting method (with random effects) and excluding studies with no events in one of the arms the reduction was 26% (OR 0.74, 95% CI 0.59 to 0.93), compared to 28% under the Peto OR model.

The I-squared was 29% in the Peto OR specification, suggesting that 29% of the variation across studies was due to underlying variation in true odds ratios, and 71% due to sampling variation. For the frequentist model we cannot reject the hypothesis of homogeneous effects (p-value = 0.14). For the Bayesian model, the I-squared was 6% (95% CrI from 0 to 25%). A leave-one-study-out cross-validation (LOO CV) procedure for the Bayesian model suggests similar out-of-sample performance for fixed-effects and random-effects models.

Using univariate meta-regression models we did not find significant differences in effect by prevalence of diarrhea, level of compliance, unit of randomization (cluster vs household), or diarrhea effect estimates (see Fig. S5, S6, S7, S9). For the year that the intervention was implemented (Fig S8) we find an increase in log(OR) of 0.055 per year (SE = 0.029, p-value = 0.056). However, this does not correct for multiple hypothesis tests and the assumption of a linear relationship between year and logarithm of OR seems unlikely to be correct. Moreover, a simple post-hoc simulation approach (Material and Methods, section 6) suggests that power based on our sample of 15 studies is not sufficient to detect such differences, even assuming a strictly linear relationship.

Cost effectiveness

The meta-analysis suggests that free provision of water treatment can cost-effectively reduce child mortality. Below we consider the cost of two delivery methods for water treatment, which we estimate would have a cost-effectiveness of around $36 per DALY averted.

Several multilateral organizations produce lists of the most cost-effective, evidence-backed health approaches, and recommend that governments prioritize these approaches for investment.

Perhaps in part due to a lack of randomized evidence on the effect of water treatment on child morality, often these lists exclude or de-prioritize water treatment.

In some cases, water treatment is excluded from these lists, presumably in part due to insufficient evidence on child mortality impacts. For example, the WHO's WHO-CHOICE analysis compares cost-effectiveness across diseases and health programs, and lists a subset of the most cost-effective interventions for maternal, newborn and child health. The latest update (107) lists 39 interventions for sub-Saharan Africa with a cost of less than $100 per healthy life year, including childhood vaccination (8 interventions), family planning, antenatal care and birth attendance (10 interventions) and malaria treatment. It lists a further eight interventions with a cost of less than $1,000 per healthy life year. It does not include water treatment or water quality.

The World Bank's Disease Control Priorities 3 does include water treatment. However, whilst its cost-effectiveness estimate ($180 - $200 per DALY) (108) is well below the WHO's threshold, it is 5 - 6 times lower than the estimate in this meta-analysis, and does not put water treatment in one of the higher categories of cost effectiveness (<$100 or <$10 per DALY).

Point-of-access chlorine dispensers

Cost data was provided by the NGO Evidence Action, which has programs in Kenya, Uganda and Malawi. We focus on Kenya, where Evidence Action operated approximately 18,400 point-of-collection chlorine dispensers as of 2020, providing roughly 2.19 million people with access to safe water. Given an adoption rate of 52%, approximately 1.14 million people are estimated to treat their water (34). The cost data coupled with the Peto OR meta-analysis estimate of the child mortality impact of water treatment across all interventions (OR = 0.72), imply a cost per DALY averted due to water treatment of USD 36 (see Table 2 Column 1), far lower than Kenyan GDP per capita (about USD 1,838 in 2020), which is the threshold suggested by the WHO to determine if interventions are "highly cost-effective". A more detailed discussion of the cost-effectiveness calculation has been provided in the supplementary material (Materials and Methods, section 3).

Coupons for free dilute chlorine solution

While dispensers achieve relatively high usage rates, they are only suited to contexts in which sufficiently many households use each water source. Programs providing coupons for free dilute chlorine solution to families with young children may have wider applicability. Because such programs have so far only been conducted at a modest scale, it is difficult to assess costs for

large-scale programs, but back of the envelope calculations suggest coupons would also be highly cost effective (see Table 2 Column 3) (35, 36). A 150-milliliter bottle of dilute chlorine solution sufficient for treating one household-month of water costs USD 0.30. If for every two households targeted the program covers an additional untargeted household which already has clean water, and if the administrative costs of running a coupon program were as large as the retail price of the chlorine solution, the cost of a scaled-up program would still only be USD 2,675 per death of a child under 5 averted – or USD 34 per DALY averted.

Rough calculations suggest that a global coupon program which provides coupons for free chlorine solution to all families with under 5 children without access to safe drinking water in low- and middle-income countries could avert up to half a million under five deaths each year (see Table S7). The WHO estimates that 2.2 billion people around the world do not have access to safely managed drinking water services (1), see row 1 (Table S7), similar in magnitude to the global estimates from other studies (37, 38). A rough back-of-the-envelope calculation, adjusting the meta-analysis estimate of improved water quality on child mortality (OR 0.72) for coupon usage rates, suggests that a program that targets this population would save approximately half a million under-five lives at a cost of just around USD 1 billion each year. This gives a sense of the order of magnitude of costs and benefits one could expect if water treatment were made universally available through a coupon program.

Discussion

Present analysis

The meta-analysis of fifteen water treatment RCTs estimates a cross-study reduction of about 30% in the odds of child mortality. Estimates from two illustrative programs suggest that water treatment is among the most cost-effective ways to improve child health. Our cost-effectiveness estimates of $34 - $36 per DALY averted would rank water treatment among the most cost-effective interventions according to either WHO-CHOICE or the World Bank's DCP-3. Other interventions with a cost per DALY of $10 - $100 include micronutrient interventions, insecticide treated malaria bed-nets, and routine childhood vaccinations.

Even much smaller effects would be cost effective according to the WHO criterion. For example, repeating the calculation for chlorine dispensers (Table 2) we find that cost-effectiveness threshold (1,838 USD per DALY) is reached at 0.6% reduction in odds of under 5 mortality.

Model limitations

Like in all meta-analyses, the main estimate we obtain in this study is specific to the sample of included studies. While we assume a model with heterogeneous effects, estimated heterogeneity across the fifteen RCT studies is not large and we cannot reject the hypothesis of a homogeneous treatment effect. We check for heterogeneous effects through subgroup analyses and meta-regression, but, as demonstrated above (for the cases of prevalence, compliance, and year of implementation) we have limited power to assess this. This fact can also be grasped intuitively by considering that despite large variation across estimates from individual studies, most of that variation is attributable to sampling. Therefore it is possible that the effect of water treatment varies radically depending on some group of parameters.

However, it is also worth noting that the studies included in this meta-analysis are broadly representative of the settings in which policymakers might implement water treatment programs, along several major characteristics. In particular, estimates of diarrhea prevalence among the included studies are representative of prevalence in low- and middle-income countries. We also don't find any substantial differences between our subset of 15 studies and a larger population of RCTs of water treatment.

Further, while we found no statistical evidence of publication bias, these tests may have limited power. The adjusted estimate obtained using Andrews and Kasy method was higher than our main estimate (OR = 0.83) but still implied high effectiveness of water interventions. While we included all data for which authors reported that mortality data were collected and remained available, there is still a risk of publication bias if authors were more likely to collect data, preserve data, or answer positively regarding the existence and availability of data in situations in which effect sizes were likely to be larger. To address this issue, in the future version of the paper we will conduct simulations based to understand how different levels of publication bias would affect the results. We will base this assessment on studies which measured diarrhea but not mortality outcomes to obtain realistic sample sizes and follow-up durations. For this version of the paper we have included an exploratory simulation of the impact of potential mortality publication bias in shorter studies, reasoning that short studies are most likely to not report on mortality data due to low event rates. We find that even if 15 studies with 3-month follow-up and a null effect were added, the mean OR estimate would still be 0.81 and statistically significant (Materials and Methods, section 5).

The studies included in the meta-analysis have differing lengths of follow-up, ranging from 9.5 to 260 weeks. The collective weight of studies that are shorter than 1 year (5 out of 15) is about

10% for both models and simulations show that the impact of including more short studies on precision of the estimate is negligible (Materials and Methods, section 2). Implicit in our model is an assumption that odds measured in the included studies, sometimes of short duration, can be interpreted as odds of under-5 mortality. This would be an acceptable choice if the odds-ratio treatment effect is homogeneous with age, which is something we do not examine in the present analysis of aggregate data.[1] Survival modeling methods could be used to address this, but it will require novel modeling approaches that can combine summary-level data with survival models based on individual-level data, since the latter are available for a subset of studies only. In the next version of the paper we will include exploration of age distributions and how baseline risks vary with age for that subset of studies.

Comparing meta-analysis estimates with model predictions

The point estimate of the mortality effect from the meta-analysis is larger than the point estimate predicted by a simple model in which diarrheal deaths are taken from the central estimate of the Global Burden of Disease (GBD) project (2), the effect of water treatment on diarrhea is taken from the central estimate in the Clasen meta-analysis (8), and mortality is assumed to be linear in diarrhea cases, so reductions in diarrhea deaths are proportional to reductions in diarrheal cases. However, the differences are small enough that they could fairly easily be accounted for by known epidemiological factors not captured by this simple linear model and sampling variation

A recent Cochrane review (8) found a reduction in under-five diarrhea due to water quality interventions of 39% (CI 95% 25%, 51%).[2] Under a simple model in which deaths are approximated as linear in cases and cases are estimated as linear in treatment rates, multiplying the central GBD estimate of the proportion of under-5 deaths attributable to diarrhea of 9.9% (CI 95% 8.2%, 11.6%) times the central Cochrane estimate of 39% gives a predicted 3.9% mean reduction in child mortality from water treatment. If we interpret the two CIs above as Bayesian intervals, the 95% interval on this estimate is 2.6% to 5.5%. In contrast, the meta-analysis in this

[1] Even under a correctly specified model and unbiased estimate, treating ORs from short studies as ORs over 5 years will slightly bias the estimate in direction of no effect, due to compounding of risks. However, the bias this introduces is small, e.g. ORs will differ less than 0.01 even when comparing a 13-week to a 260-week study.

[2] This confidence interval reflects sampling variation only, but estimated effects of water treatment on caregiver-reported diarrhea may also be subject to reporting bias (8, 9).

paper gives a central estimate of an approximately 30% reduction in the odds of all-cause child mortality.

One likely reason for differences between the predictions of a simple linear model and the meta-analysis findings is that several scientifically plausible pathways through which water treatment could reduce mortality are not captured by the linear model.

First, water treatment could reduce both the mortality rate and the incidence of diseases other than diarrhea (Mills-Reincke phenomenon) (39, 40). Epidemiological studies lend support to this hypothesis, showing that diarrheal episodes are followed by increased risk of acute lower respiratory tract infection among children in Ghana, Nepal, India, Pakistan and Israel (32, 41 - 43). Continued exposure to diarrheal pathogens alters the gut microbiome, increasing susceptibility to infection (44). Such subclinical or clinical episodes of infection can induce impairments in gut function and undernutrition phenotypes leading to increased mortality (45, 46). Relatedly, diarrhea can lead to malnutrition (47, 48), which in turn can put a child at risk for higher mortality from a range of illnesses, or simply death from malnutrition itself. The Global Burden of Disease uses a "one death one cause" methodology, which allows it to estimate all causes of deaths without double counting. However, it could under-estimate the mortality effect of addressing a given disease in scenarios like this, where morbidity from multiple diseases combines to cause a death.

Second, water treatment could prevent diseases which can cause life-threatening illness in the absence of diarrhea. It could reduce worm loads; kill enteroviruses, *Salmonella Typhi* and *Salmonella Paratyphi*, and prevent hepatitis A and hepatitis E. Water treatment could also prevent deaths from sepsis among infants by facilitating cleaner births and postnatal care practices (49). Poor water quality and exposure to a more pathogenic environment is associated with preterm birth and low birth weight (50).

Third, water treatment could potentially have a larger effect on severe diarrhea than on overall diarrhea. This is the case for some other interventions. For example there is evidence that RRV-TV rotavirus vaccines lead to greater reductions in severe diarrhea episodes than in mild ones (10, 11). Another example is COVID-19 vaccines, many of which have been far more effective against hospitalization and death than infection.

Fourth, the GBD estimates Estimates of the diarrheal death rate are limited by data availability, requiring modeling to fill data gaps, and according to the authors, many datasets have biases or errors, such as the misclassification of causes of death or assignment of deaths to causes that

cannot be primary causes of death (51). For example, estimated effects of water treatment on caregiver-reported diarrhea may be subject to reporting bias (32, 52).

There is also uncertainty in our estimates and in the estimates from the Clasen et al. meta-analysis, although the portion of uncertainty due to sampling variation in these is more easily quantified.

Considering other sources of evidence

In estimating effects of interventions to improve water quality on mortality, other sources of evidence could be used in the future to supplement estimates based on RCT evidence. Estimates of effects from a review of quasi-experimental literature could be considered. A more sophisticated model could incorporate Global Burden of Disease (GBD) estimates of diarrheal rates, meta-analysis estimates of reductions in diarrhea rates associated with water treatment, nonlinearities due to epidemiological factors and differences in the responsiveness of diarrhea and severe diarrhea to water quality interventions, and possible pathways beyond diarrhea. This could be done formally by encoding them as priors in a Bayesian meta-analysis model. However, a careful consideration needs to be given to uncertainty and interpretation of these additional sources of information, to ensure generalizability, appropriate weighting of different sources of evidence, and to avoid overconfidence in the final estimate.

As discussed above, the linear model likely underestimates the impact of interventions to improve water quality on child mortality. However, even under the predictions from this model, chlorine dispensers would remain seven times more cost-effective than WHO's "highly cost-effective" threshold at USD 247 per DALY averted (see Table 2 Column 2). Thus, independent of the tightness of their priors, an analyst who starts with priors based on the linear model and updates based on evidence from this meta-analysis would conclude that water treatment is also cost-effective.

Lists of cost-effective health approaches

Lessons for meta-analysis and pre-analysis plans

Methodologically, our results suggest that meta-analysis may be important for assessing effects which are small in absolute magnitude yet potentially large enough to be highly cost-effective. Unfortunately, multiple hypothesis testing requirements could potentially discourage authors from reporting outcomes for which power is low.

At the beginning of this study, five RCTs were identified which reported mortality outcomes as part of their analysis (23, 29, 30, 53, 19). The estimates from restricting the analysis to only the five studies which published mortality outcomes were similar in magnitude to that of the full sample though insignificant at the 95% confidence level (Peto OR 0.67; CI 95% 0.41, 1.11; Bayes OR 0.73; CrI 95% 0.28, 1.44). By including studies which did not report mortality outcomes, we are able to increase statistical power to detect significant effects in our main results (see Table S4). However, this necessitated a time-consuming process of contacting authors to request the data and led to the loss of some data that was once available but is no longer available. One potential reform would be for pre-analysis plans to include a section listing outcomes for which the study is underpowered, but which will be reported for use in meta-analyses, and for individual studies to report such data, but not to be expected to conduct multiple hypotheses testing on such outcomes. Committees of scholars in the field could recommend a limited set of rare but important and easy to collect outcomes such as mortality for collection and incorporation in meta-analyses.

Data sharing

All data and code to replicate the results (figures and tables) of this meta-analysis has been made publicly available.

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Declaration of interests

None of the authors have a conflict of interest or any financial conflict to disclose.

Supplementary materials

Materials and Methods

Figs. S1 to S8

Tables S1 to S11

Data

Risk of bias table

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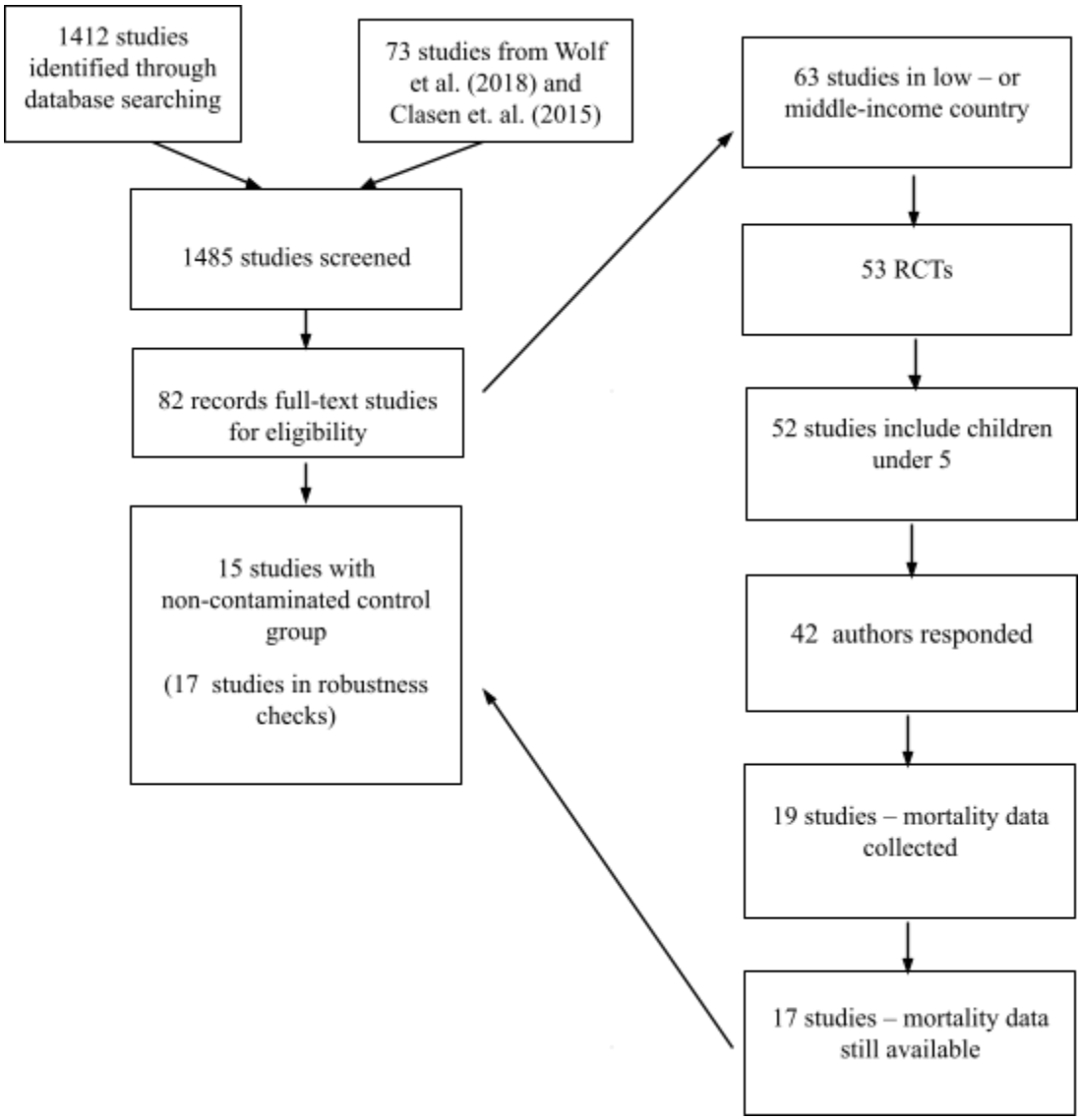
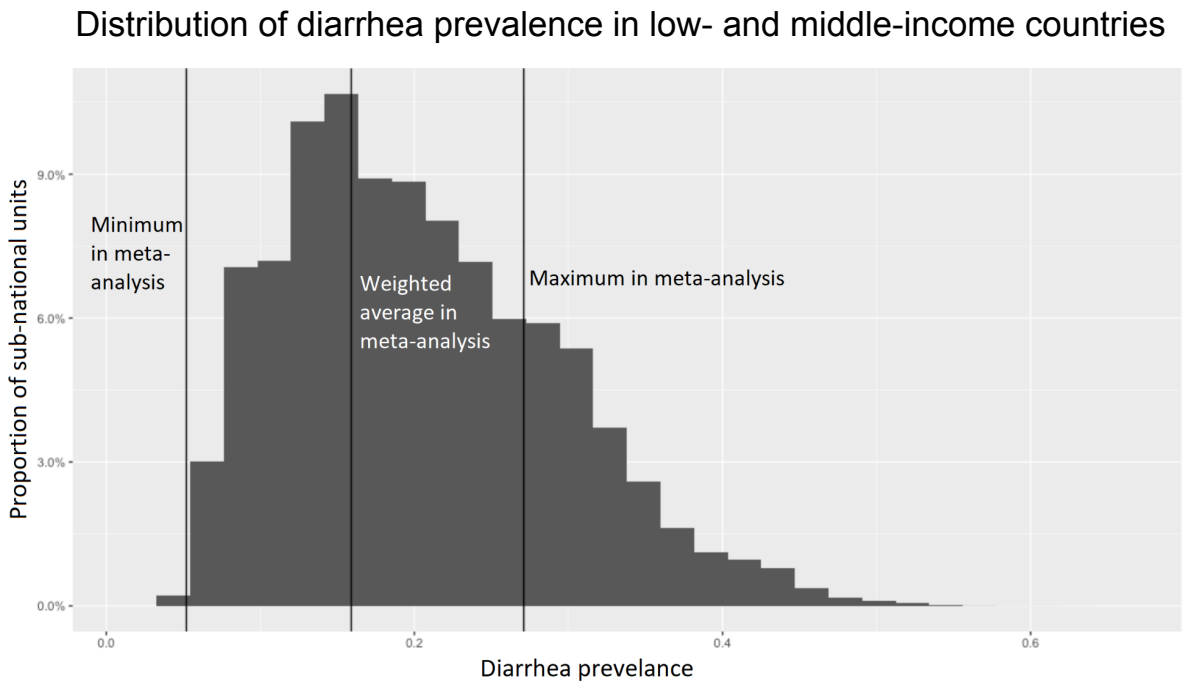
Figures and Tables

Fig. 1. Study selection



Note: This funnel chart depicts the search strategy and selection criteria for studies included in the meta-analysis. Non-contamination of control groups was added as an inclusion criteria after reviewing the studies and was not decided prior to the review of studies.

Fig. 2. Distribution of diarrhea prevalence in low- and middle-income countries

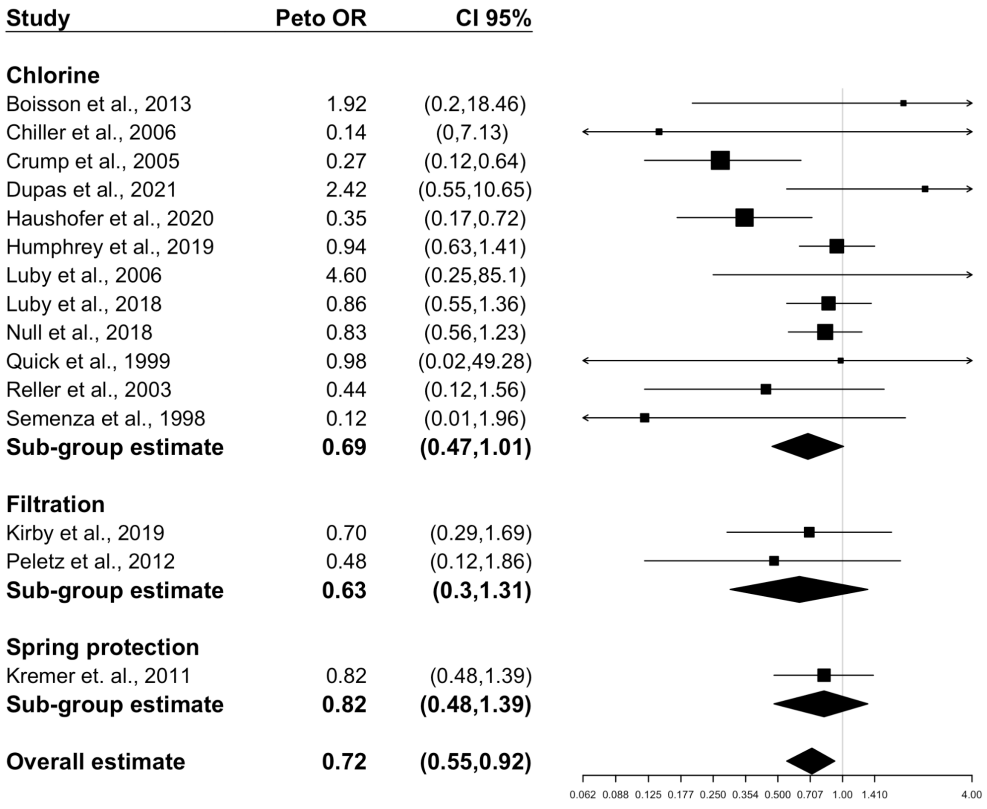


Note: This histogram shows diarrhea prevalence (%) across sub national geographic units of 94 low- and middle-income countries as of 2017. Black lines indicate the minimum, weighted average, and maximum diarrhea prevalence in studies included in the meta-analysis.

Source: Institute for Health Metrics and Evaluation, 2020 (28)

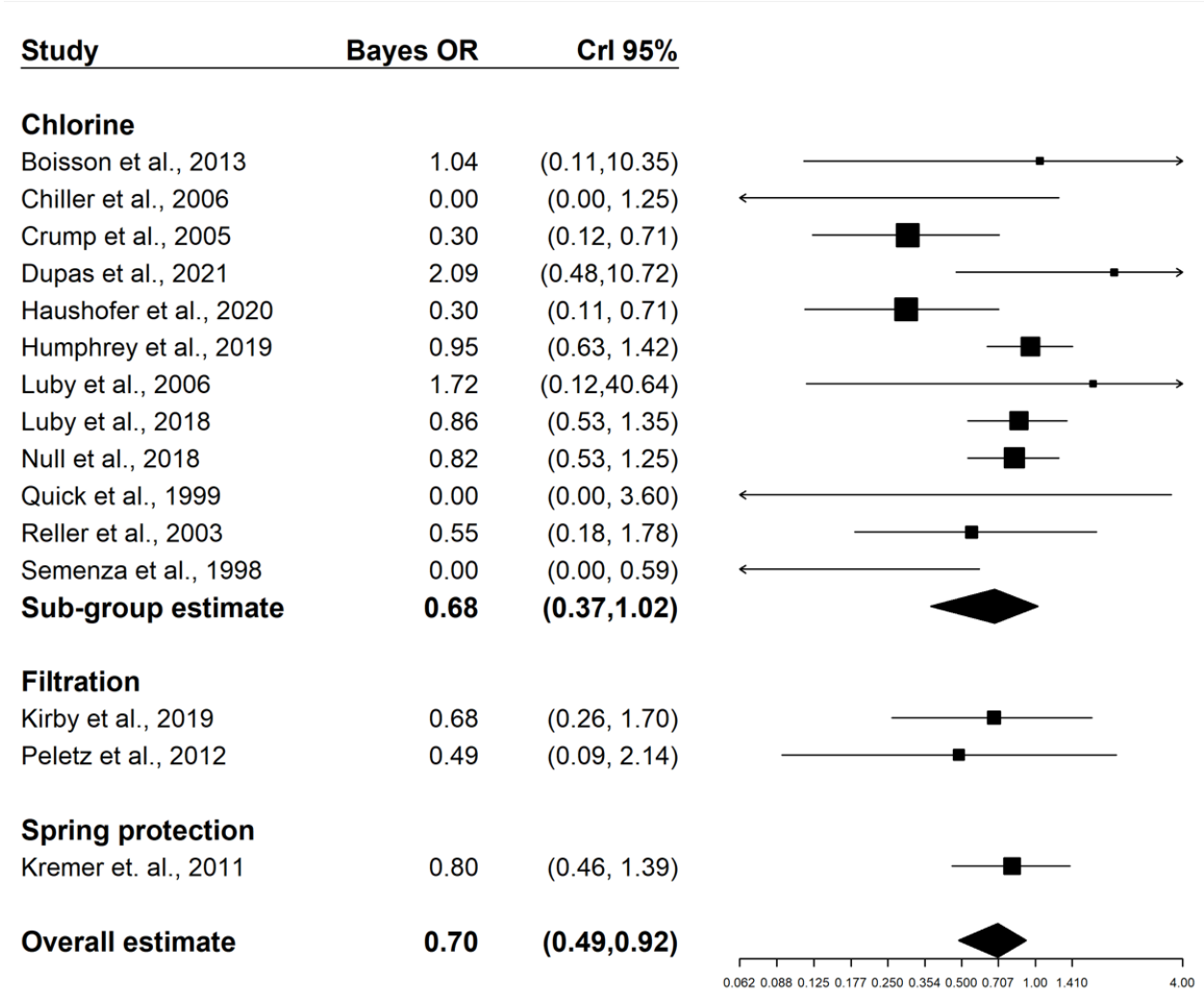
Fig. 3. Forest plots of meta-analysis results

(A) Peto Odds Ratio



Note: Dots and horizontal lines represent mean estimates and their 95% confidence intervals from individual studies. Estimates for individual studies are Peto odds ratios. The size of each dot represents the weight given to the study. Diamonds are centered around the meta-analysis estimates and their widths indicate the 95% confidence/credible interval. In addition to the overall estimate we also show estimates for subgroups of studies by intervention type.

(B) Bayesian Odds Ratio



Note: Dots and horizontal lines represent posterior means and 95% credible intervals: for individual studies they are the ORs under Bayesian no pooling model, for chlorine studies and overall estimates they are the estimates from partially pooled (random effects) model. See Materials and Methods, section 1 for details, including choice of priors. We do not report the Bayesian OR for the subset of filtration studies because we only have two filtration studies in our sample and the parameters of the Bayesian hierarchical model are not well-identified in that case.

Table 1. Summary of studies included

Study	Intervention	Sample size	Country	Population of study	Obs. period	Infectious environment indicators		Compliance rate	(a)	(b)	(c)	(d)
						Contamination levels	Diarrhea prevalence					
A. Main sample												
Semenza et al., 1998 (54)	Chlorination	(Chlorination) 68 households, (Control) 58 households	Uzbekistan	Households with an <5y old child	9.5 weeks	54 TTC/100 ml pre-treatment	12.77% in control children	73.0%	0	88	2	78
Reller et al., 2003 (20)	(1) Flocculant-disinfectant, (2)	(1) 102 households,	Guatemala	Households with an ≤11m old	1 year	Concentration of E.	13.2% in control	(1) 27%, (2) 34%,				

	Flocculant-disinfectant + vessel, (3) Chlorination , (4) Chlorination + vessel	(2) 97 households (3) 97 households, (4) 100 households, (Control) 96 households		or pregnant woman in third trimester		coli per 100ml: 63	children (≤12m)	(3) 36%, (4) 44%	10	729	5	182
Crump et al., 2005 (30)	(1) Chlorination, (2)Flocculant-disinfectant	(1) 203 households, (2) 201 households, (Control) 201 households	Kenya	Family compounds with at least one child <2y old	20 weeks	Concentration of E. coli per 100ml: 98 (mean at baseline); Share of households meeting WHO water quality standard: 14% in control	9.6% in control children; 2.7% in control group (all ages)	52.5%	9	1009	15	505

Luby et al., 2006 (19)	(1) Chlorination, (2)Flocculent-disinfectant water treatment	(1) 265 households (2) 262 households (Control) 282 households	Pakistan	Households with an <5y old child	37 weeks	Diarrhea is a leading cause of death and the environment is heavily contaminated with sewage	8.62% in control group	Unavailable	2	1013	0	553

Chiller et al., 2006 (55)	Chlorination	(Chlorination) 1702 individuals, (Control) 1699 individuals	Guatemala	Households with an <1y old child	13 weeks	98% drinking water sources contaminated with E. coli at beginning of study	6% in control group	85.0%	0	132	1	137
Kremer et. al., 2011 (56)	Spring protection	(Spring protection) 749 households, (Control) 685 households	Kenya	Households which use selected springs	2 years	Concentration of E. coli per 100ml: 44.3	20% in control children	69.0%	18	691	47	1465

Peletz et al., 2012 (53)	Filtration	(Filtration) 61 households, (Control) 59 households	Zambia	Households with a 6m-1y old at enrollment and with HIV+ mothers (100 HIV+ and 20 HIV-)	1 year	181 TTC/100ml for control (endline)	13.6% in control children (<2 y)	87.0%	3	58	6	54
Boisson et al., 2013 (56)	Chlorination	(Chlorination) 1080 households, (Control) 1083 households	India	Households with an <5y old child	1 year	122 TTC/100 ml in control over the course of the study	5.2% at baseline for children (<5 y)	32.0%	2	1505	1	1507

Null et al., 2018 (17)	Chlorination	(Chlorination) 904 households, (Control) 1913 households	Kenya	Newborns	2 years	>75% of household collected water from improved water sources at baseline	27.1% in (active) control group*	30.0%	30	858	114	2697
Luby et al., 2018 (29)	Chlorination + vessel	(Chlorination + vessel) 698 households , (Control) 1382 households	Bangladesh	Newborns and their siblings under 36m old	2 years	74% collected drinking water from shallow tubewells at baseline	5.7% in control group	81.0%	27	629	62	1244
Humphrey et al., 2019 (22)	Chlorination + sanitation + hand washing + play space + hygiene counselling + construction of	(WASH) 918 children, (Control) 884 children	Zimbabwe	Households with an <18m old child	1.5 years	63% of household collected water from improved water	9.5% in control	79%	49	946	50	909

	improved pit latrines (WASH)						sources at baseline					
Kirby et al., 2019 (21)	Filtration + Cookstoves	(Filtration + Cookstoves) 87 villages, (Control) 87 villages	Rwanda	Households with an <5y old child	1.25 years	>100 TTC/100 ml for 38% of households in control	12.9% in control	69.9%	8	1198	12	1252
Haushofer et al. 2020 (18)	Chlorination (follow-up to Null et al., 2018)	(Chlorination) 65 villages, (Control) 67 villages	Kenya	Children <5y	4-6 years	>75% of household collected water from improved water sources at baseline	27.1% in (active) control group*	31.0%	7	987	22	965

Dupas et al. 2021 (36)	(1) Coupons for chlorination (subsidy) (2) Coupons + free delivery + WASH (3) Coupons + WASH (4) WASH	(1) 441 households (2) 458 households (3) 468 households (4) 468 households (Control) 460 households	Malawi	Households with an <6y old child	61 weeks	70.7% of household collected water from a protected water source at baseline	12.4% in control group	40%	5	1288	2	1321
Quick et al. 1999 (58)	Chlorination + safe storage of treated water + community education	(Chlorination + safe storage of treated water + community education) 400 individuals, (Control) 391 individuals	Bolivia	All households in study communities	34 weeks	Median *E. coli* colony count for well water (baseline): 34/100 ml and for stored water (baseline): 44/ 100 ml	38.0% in control group	71.0%	0	400	0	391

B. Studies included for robustness checks											
Boisson et al., 2010 (24)	Filtration	(Filtration) 546 individuals, (Control) 598 individuals	Democratic Republic of Congo	All households in selected communities	1 year	75% of source water samples had >1,000 TTC/100 ml	8.96% in control children (<5 y)	68.0%	4	81	1	104
du Preez et al., 2011 (26)	Solar disinfection	(Solar disinfection) 579 children, (Control) 554 children	Kenya	Children 6m-5yo	1.5 years	Most households collected water from standpipes (with treated water)	5.2% of dysentery in control	68.0%	3	355	3	334

Note: * In Null et al., 2018 (27) there was an active control group which received enumerator visits and a passive control group with no visits.

(a). Counts of events in treatment group

(b). Counts of non-events in treatment group

(c). Counts of events in control group

(d). Counts of non-events in control group

Table 2. Cost–effectiveness analysis

		Chlorine Dispensers in Western Kenya		**Global Coupon Program**		
		Meta-analysis	*Linear model*	*Meta-analysis*	*Linear model*	Sources
(1)	Intent-to-treat (OR) estimate of the provision of water treatment on child mortality	0.72	0.96	0.72	0.96	This study[a]; Global Burden of Disease Study, 2019 (2)
(2)	<5y mortality rate (in pp)	6.90	6.90	5.00	5.00	Dispensers: Kenya DHS, 2014 (105)[b:] Coupons: UN Interagency Group for Child Mortality Estimation (106)[c]
(3)	Intent-to-treat estimate of the provision of water treatment on <5y mortality (in pp)	-1.90	-0.30	-1.40	-0.20	X/(X+1) - (2), where X = (1) * ((2)/1 - (2))

(4)	Intent-to-treat estimate of the provision of water treatment on <5y mortality, per year (in pp)	-0.40	-0.10	-0.30	-0.04	(3) / 5 years
(5)	Average take-up in meta-analysis	0.59	0.59	0.59	0.59	This study
(6)	Average take-up rate in intervention	0.51	0.51	0.32	0.32	Dispensers: Evidence Action (62); Coupons: mean across Dupas et al., 2016 (35) and Dupas et al., 2020 (36)
(7)	Expected effect of water treatment on <5y mortality, per year (in pp)	-0.30	-0.05	-0.10	-0.02	Calculated as (4)*(6)/(5)
(8)	Cost per child <5y served, per year (in USD)	9.1	9.1	4.0	4.0	Dispensers: Evidence Action (43)[d];

						Coupons: Dupas et al., 2016 (35) and Dupas et al., 2020 (36)[e]
(9)	Cost per death of a child <5y averted (USD)	2811	19567	2675	18895	Calculated as -(8) / ((7) / 100)
(10)	Cost per DALY averted	35.5	247	33.8	238	Calculated as (9) / DALYs lost from child death <5y[f]

[a] Meta-analysis estimate is from Table 2 Column 2 of this study; the linear model estimate is based on multiplying the global fraction of child deaths due to diarrhea by the percentage reduction in diarrhea associated with water treatment

[b] <5 mortality rate weighted by the % of dispensers present in that region.

[c] <5 mortality rate across countries weighted by population without access to safe drinking water.

[d] Average cost over the 2016-2017 period

[e] 0.30 USD (Retail cost per bottle of chlorine) * 2 (Assumption that administrative costs are as large as the price of chlorine bottles) * 12 months * 0.37 (Share of coupons redeemed) * 1.5 (Assumption that for every two households with a child <5y without access to safe drinking water, one untargeted household receives coupons. 0.37 is the average share of coupons redeemed across Dupas et al., 2016 (44) and Dupas et al., 2020 (45).

[f] The number of DALYs lost from death under 5 assumes a life expectancy of 81.25 years and average age at death of 2, following the standard approach of calculating DALY outlined in "WHO methods and data sources for global burden of disease estimates 2000-2019" (140).