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Linking Quantitative Microbial Risk Assessment and Epidemiological Data: Informing Safe Drinking Water Trials in Developing Countries

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Supporting Information

ABSTRACT: Intervention trials are used extensively to assess household water treatment (HWT) device efficacy against diarrheal disease in developing countries. Using these data for policy, however, requires addressing issues of generalizability (relevance of one trial in other contexts) and systematic bias associated with design and conduct of a study. To illustrate how quantitative microbial risk assessment (QMRA) can address water safety and health issues, we analyzed a published randomized controlled trial (RCT) of the LifeStraw Family Filter in the Congo. The model accounted for bias due to (1) incomplete compliance with filtration, (2) unexpected antimicrobial activity by the placebo device, and (3) incomplete recall of diarrheal disease. Effectiveness was measured using the longitudinal prevalence ratio (LPR) of reported diarrhea. The Congo RCT observed an LPR of 0.84 (95% CI: 0.61, 1.14). Our model predicted LPRs, assuming a perfect placebo, ranging from 0.50 (2.5−97.5 percentile: 0.33, 0.77) to 0.86 (2.5−97.5 percentile: 0.68, 1.09) for high (but not perfect) and low (but not zero) compliance, respectively. The calibration step provided estimates of the concentrations of three pathogen types (modeled as diarrheagenic *E. coli*, *Giardia*, and rotavirus) in drinking water, consistent with the longitudinal prevalence of reported diarrhea measured in the trial, and constrained by epidemiological data from the trial. Use of a QMRA model demonstrated the importance of compliance in HWT efficacy, the need for pathogen data from source waters, the effect of quantifying biases associated with epidemiological data, and the usefulness of generalizing the effectiveness of HWT trials to other contexts.

INTRODUCTION

Diarrhea is a major cause of infectious disease mortality, accounting for 17% of deaths in children under 5 years of age; only pneumonia accounts for a similarly high share of mortality in this age group.[1] Diarrheal mortality has declined from approximately 5 million in 1980[2] to 2 million in 2000 and 2004.[3,4] However, the incidence of diarrhea has remained at 2−3 episodes per child-year from 1980 to 2000.[2,5,6]

Contaminated drinking water is an important route of transmission for diarrheal pathogens. Recent reviews indicate that household water treatment (HWT) interventions, which can improve microbiological quality at the point of use, can be more protective against diarrhea than interventions at the water source in the developing world.[7−10] HWT addresses not only contamination of the source water, but also recontamination during collection, transport, and storage in the home.[11] The long-term sustainability and scalability of HWT remain important issues of discussion.

The randomized controlled trial (RCT) is considered the gold standard study design in epidemiology; it is the study design with the least systematic bias, and therefore the highest internal validity. Two important components of RCT design for internal validity are the randomization of subjects to the intervention and the nonintervention groups, and blinding of the subject and investigator to group assignment. It is difficult to blind HWT interventions because these devices are visually obvious and cannot be concealed from participants or investigators. It is also difficult to develop a placebo HWT filter that does not remove pathogens, but improves the appearance of water like an effective filter.[12] Other biases may also affect the internal validity of an estimate derived from the

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trial, such as recall bias, incomplete compliance with the intervention, or unexpected difficulties conducting the trial.[12]

In a recent RCT[12] in rural communities in the Democratic Republic of the Congo (DRC) using the LifeStraw Family Filter (LFF; Vestergaard Frandsen Corporation, Lausanne, Switzerland), investigators attempted to blind the intervention. The LFF is an ultrafilter with a 20-nm pore size that was shown to remove 99.99999% of *Escherichia coli*, 99.998% of *Cryptosporidium* oocysts, and 99.97% of MS2 coliphage from challenge water in the laboratory.[13] For the Lifestraw RCT, investigators developed a placebo filter resembling the LFF in appearance, weight, operation, and flow rate.[12] The placebo was tested in the laboratory for three weeks against the same three organisms, and no removal was observed. In the field, however, the intended placebo removed on average 91% (95% CI: 88–93%) of thermotolerant coliform bacteria (TTC), a group that includes *E. coli* and indicates fecal contamination, from source water.[12] Therefore, the study could only compare a highly effective filter with a poorly effective filter. Although 65% of people reported using the filter, most filter users also reported drinking unfiltered water.[12] The proportion of unfiltered water that people consumed was not quantified. The Lifestraw RCT did not find a statistically significant ($P < 0.05$) effect of the LFF against diarrhea.[12]

Quantitative microbial risk assessment (QMRA) models can examine and account for biases associated with environmental intervention trials (e.g., imperfect compliance, recall bias, or an imperfect placebo) and can explore risks associated with different contexts from those observed in empirical studies. Such models can provide a conceptual framework for understanding systems that are difficult to explore in the real world. QMRA models have been used to quantify disease risk in many contexts.[14−16] Our analytic framework for HWT and approach to link QMRA and epidemiological data are unique and consist of (1) a calibration step using a QMRA model to produce results consistent with the epidemiological study; and (2) an estimation step that examines counterfactual scenarios that adjust for biases within the study and explores how altered contexts affect risk. The effectiveness of an intervention in those contexts can then be estimated, even if it was never directly studied under such conditions.

In this manuscript we develop a counterfactual causal inference framework using a QMRA model to evaluate the impact of biases on estimates of intervention efficacies. We illustrate the approach by simulating the Lifestraw RCT[12] and adjusting for some of its biases, to estimate the effectiveness of the LFF compared with a perfect placebo under differing levels of LFF compliance.

MATERIALS AND METHODS

Conceptual Framework Linking QMRA Models to Epidemiological Studies. Quantitative microbial risk assessment (QMRA) uses environmental contamination data as input to models used to predict risk of infection or disease. Epidemiological studies provide data on patterns of disease measured by incidence or prevalence and measures of relative risk. Here we provide a framework for the calibration of risk models by using epidemiological data from a particular study that describes the risk in a particular context, where the context is defined by a particular time in a particular geographic setting (Figure 1). The calibration process involves simulating a risk model many times using different input and parameter values. The parameter sets (or parameter distributions) representing

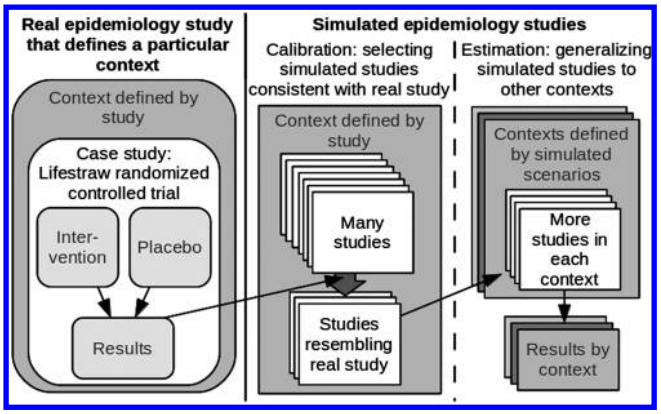

Figure 1. Conceptual model linking QMRA models to epidemiological studies. The results from an actual epidemiology study define a context (e.g., the LifeStraw Family Filter randomized controlled trial [Lifestraw RCT] in rural Congo). The calibration phase generates a set of simulated studies that are consistent with this defined context. Calibration also estimates values for parameters that were not observed during the real study, thus inferring unobserved context of the real study. The estimation phase generates simulated studies that are generalized to other contexts (e.g., higher or lower compliance than was observed during the Lifestraw RCT). For more detail, see Supporting Information (SI), Figure S1.

simulations that are consistent with the epidemiological study comprise the calibrated model; the parameter distributions provide a representation of the context in which the epidemiological study was conducted. Using this calibrated model, the epidemiological study can be generalized to other contexts in what we call the estimation step. This estimation step, therefore, consists of a set of simulations in which specific parameter values are varied to describe different contexts, such as alternative intervention strategies or different ecological or social settings.

For the research described herein, a QMRA model was developed that simulates the following chain of events:

1. Determination of the concentrations of three pathogen types (bacteria, protozoa, and viruses) in drinking water, sampled from gamma distributions
2. Calculation of daily doses of pathogens based on their concentrations and the amount of water consumed
3. Use of dose response functions to convert daily doses of pathogens to probabilities of infection
4. Assignment of infection to individuals, based on the probabilities of infection
5. Assignment of diarrheal illness, based on morbidity ratios

The same conceptual approach illustrated in Figure 1 could also be applied to more complex models including processes such as transmission dynamics[17,18] or environmental fate and transport dynamics.[19]

Case Study Model Description. The model describing the Lifestraw RCT conducted in the Congo[12] follows a simulated population of children under 5 years of age for 12 months using a time unit of 1 day (for details, see Supporting Information (SI), Section A and Figure S1). The population is surveyed about their diarrheal symptoms every 4 weeks, similar to the Lifestraw RCT. The simulated children ingest bacteria, protozoa, and viruses in their drinking water, respectively represented by diarrheagenic *Escherichia coli*, *Giardia* cysts, and rotavirus. These three pathogens were chosen because they are major causes of diarrheal disease in much of the developing

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world, and they represent the three main taxa of waterborne pathogens.[20] A child is either susceptible to, immune to, or infected by each of these three pathogens; we assume that the infective processes of each pathogen are independent of each other, and a child may therefore be infected with 0, 1, 2, or 3 types of pathogens simultaneously. Children are divided into two groups, one receiving the intervention filter (with $\log_{10}$ removal values for *E. coli*, *Giardia*, and rotavirus set to 6.9, 3.6, and 4.7, respectively, based on laboratory testing[13]). The other group receiving the placebo filter with $\log_{10}$ removal values for the calibration step is set to 1.05 for all three pathogens (as a comparison during the analysis) based on coliform removal results from the Lifestraw RCT.[12] Additional discussion of the rationale for these values is provided in the SI, Section C5.

Compliance. Children's compliance with water filtration is described by two parameters: probability of using their filter, and proportion of water treated if using the filter. Low compliance was defined as 65% of children treating $^1/_3$ of their drinking water; medium compliance was 65% treating $^2/_3$; high compliance was 65% treating 100%; and perfect compliance was 100% treating 100%. Although the proportion of children who were treating water was estimated at 65% during the Lifestraw RCT, the proportion of water treated was not measured, so $^1/_3$, $^2/_3$, and 100% were chosen for illustration.

Estimation of Environmental Concentration and Daily Dose. The daily dose of each pathogen type for each person is determined as follows:

$$\text{Daily dose} = cd[(1 - w) + w10^{-r}] \quad (1)$$

where c is the concentration per liter of a pathogen type in untreated water (sampled from a gamma distribution), d is the liters of water consumed daily, w is the proportion of water treated (which varies depending on compliance), and r is the $\log_{10}$ reduction value (which varies depending on whether the intervention filter, the placebo filter, or no filter is being used).

Dose Response (Assignment of Infection and Disease). The daily dose is converted to a probability of infection using a dose response function[21] (SI, Section A5 and Figure S4), for children who are susceptible to that pathogen type. The probability of infection is then used to randomly determine which children become infected on that day. The duration of infection is determined by sampling from appropriate distributions (SI, Sections A7 and C2). Morbidity ratios (proportion of infected who have diarrhea) are used to randomly determine diarrheal illness given infection. Immunity is incorporated in the model in two ways: (1) complete immunity to infection from that pathogen type for 7 days after recovery from infection, followed by complete susceptibility; (2) within the morbidity ratios, because immunity to some diarrheal pathogens confers resistance to illness rather than immunity to infection (SI, Sections C1 and E4).[22−24] The morbidity ratios were obtained from studies of diarrheal disease in developing countries.[25−27]

The model estimates reported diarrhea in a manner similar to the Lifestraw RCT. It simulates a survey every 30 days that asks every child whether they had any diarrhea during the previous 7 days. The model assumes recall is perfect for the first 2 days and declines thereafter (SI, Section A8) to adjust for recall bias. We assume recall bias is nondifferential because the Lifestraw RCT was blinded.

The primary output of the model is longitudinal prevalence (LP) of diarrhea. LP is person-time diseased divided by person-time observed, as determined by the simulated surveys. This is analogous to the LP measured by the Lifestraw RCT. Two measures of reported waterborne diarrhea are generated: the LP of reported waterborne diarrhea in the intervention group (LP_{Irwd}) and the placebo group (LP_{Prwd}). A third measure, LP_{rNW}, is the LP of reported diarrhea acquired by non-waterborne routes. Combining LP_{rNW} with LP_{Irwd} and LP_{Prwd} yields the LP of all reported diarrhea in the intervention group (LP_{Irad}) and the placebo group (LP_{Prad}); (SI Section A9 has more detail):

$$LP_{Irad} \approx (LP_{Irwd} + LP_{rNW}) \quad \text{or}$$
$$LP_{Prad} \approx (LP_{Prwd} + LP_{rNW}) \quad (2)$$

The longitudinal prevalence ratio of all reported diarrhea (LPR_{rad}) describes the effectiveness of the LFF; the preventable fraction of reported diarrhea is $1 - LPR_{rad}$.

$$LPR_{rad} = LP_{Irad}/LP_{Prad} \quad (3)$$

There are a total of 33 model parameters. Values for 26 of these parameters came from published scientific literature (SI, Table S1). Four of these parameter values were estimated by calibration: the concentrations of the three pathogen types in untreated water, and the longitudinal prevalence of reported nonwaterborne diarrhea, LP_{rNW} (Table 1). The remaining three parameters were based upon the authors' judgment. For more detail about model assumptions, see the SI, Section E.

Table 1. Uniform Distributions Used to Determine the Values of the Stochastically Varying Parameters for Each Simulation Model Run During Calibration

description	lower limit	upper limit (low calibration compliance)	upper limit (medium calibration compliance)
mean concentration per L, diarrheagenic *E. coli* in untreated drinking water	0	7.0×10^4	8.0×10^4
mean concentration per L, *Giardia* cysts in untreated drinking water	0	0.95	1.3
mean concentration per L, rotavirus in untreated drinking water	0	0.14	0.18
baseline nonwaterborne diarrhea longitudinal prevalence (LP_{rNW})[a]	0	0.0972	0.0972

[a]The upper limit for baseline diarrhea longitudinal prevalence is the upper limit of the 95% CI for LP in the <5 year old intervention group in the Lifestraw RCT.[12]

Simulation Process. The simulation was implemented in two steps: calibration and estimation (Figure 1).

The calibration step estimated the four unknown parameter values (Table 1) by constraining the model outputs to the results of the Lifestraw RCT (Table 2). The calibration, which included 100 000 runs, was conducted for two calibration compliance conditions, low and medium, because the proportion of water treated by filter users during the Lifestraw RCT was unknown but believed to be substantially less than 1. Additionally, the parameters in Table 1 were randomly sampled from uniform distributions for each simulation run. The upper limits of these distributions were chosen to ensure that the entire range of concentrations consistent with the Lifestraw RCT would be included (see SI, Section A10). If a model run yielded results consistent with the Lifestraw RCT, its set of four

Table 2. Longitudinal Prevalence Measures of Reported Diarrhea from the Lifestraw RCT[a]

measure	estimate	lower limit (95% CI)	upper limit (95% CI)
longitudinal prevalence, intervention group (LP_{Irad})	0.0749	0.0526	0.0972
longitudinal prevalence, placebo group (LP_{Prad})	0.0896	0.0673	0.112
longitudinal prevalence ratio, intervention/placebo (LPR_{rad})	0.84	0.61	1.14

[a]During calibration, for a simulation model run to be considered consistent with the Lifestraw RCT, all 3 measures had to fall between the lower and upper limits.

parameter values (Table 1) was used in the estimation step. A run was considered consistent if the LP_{Irad}, LP_{Prad}, and LPR_{rad} all fell within the 95% confidence limits reported from the Lifestraw RCT (Table 2).

The estimation step determined effectiveness given the following: (1) a perfect placebo, and (2) low, medium, high, or perfect estimation compliance. It consisted of ten model runs for each parameter set that were consistent with the Lifestraw RCT (totaling >2000 runs) for each of four estimation compliance levels, assuming a perfect placebo.

The estimation step simulated measurements of LP_{Irad} and LP_{Prad}, and their ratio LPR_{rad}, which were calculated in the same way as in the calibration step (number of monthly person-surveys reporting diarrhea during the previous 7 days, divided by the total number of person-surveys).

Differing compliance values were used in each step. In the calibration step, we use "calibration compliance" to refer to a set of compliance values that describe what probably occurred during the actual Lifestraw RCT; these are necessary to calibrate the model to the four parameter values mentioned above. In the estimation step, we use "estimation compliance" to refer to a larger set of compliance values that allow the model to make predictions for several different scenarios. Calibration compliance and estimation compliance must be considered simultaneously because different calibration compliance levels lead to different results in the estimation step.

The QMRA model was programmed in Octave 3.2; the code also runs in Matlab 7.11. The model code is available online with the SI. Results were analyzed using R 2.11; the two-tailed Wilcoxon rank sum test (α = 0.05) was used to compare distributions.

RESULTS

Calibration Step. Out of the 100 000 simulation runs in the calibration step, 210 were consistent with the Lifestraw RCT based on the criteria in Table 2 and assuming low calibration compliance with water filtration. Repeating the calibration step assuming medium calibration compliance yielded 258 consistent runs. Calibration estimated distributions for two outputs:

1. The longitudinal prevalence ratio (LPR_{rad}) distributions were similar by level of calibration compliance (Figure 2). The estimate from the Lifestraw RCT falls within the central 95% of the distributions, suggesting consistency between the model and the Lifestraw RCT. The median LPR_{rad} estimated by the model differs from the Lifestraw RCT estimate because the Lifestraw RCT is a single experiment, whereas each distribution of LPR_{rad} represents over 200 simulated experiments.

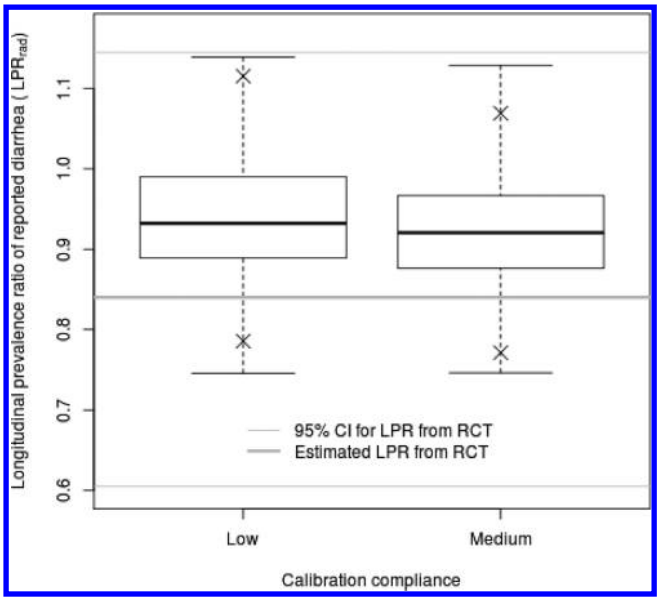

Figure 2. Distributions of longitudinal prevalence ratios from simulation runs consistent with the Lifestraw RCT from the calibration step for low (65% of children treat $^1/_3$ of their drinking water) and medium (65% of children treat $^2/_3$ of their drinking water) calibration compliance. These distributions differed significantly (Wilcoxon rank sum test, p = 0.02). Boxplots include: median (heavy line), 25th and 75th percentiles (lower and upper limits of the box), 2.5th and 97.5th percentiles (× symbols), and range (whiskers).

2. Concentrations of pathogen types in untreated water (Figure 3) were higher for medium calibration compliance compared with low calibration compliance, which is necessary to produce LP_{Irad} and LP_{Prad} values consistent with the RCT. In individual calibration runs, higher concentrations of one pathogen type were associated with lower concentrations of the other two pathogen types. The median diarrheagenic *E. coli* concentration predicted by the model is lower than the median thermotolerant coliforms (TTC) concentration measured in untreated drinking water in the Lifestraw RCT (Figure 3). This is plausible since *E. coli* are a subset of TTC, and not all *E. coli* are pathogenic.

Estimation Step. This step estimated LFF effectiveness compared to a perfect placebo for low, medium, high, and perfect estimation compliance, given low or medium calibration compliance.

Estimation compliance was a major driver of effectiveness. For example, under low, medium, high, and perfect estimation compliance, the median LPR_{rad} was 0.86, 0.70, 0.50, and 0.13, respectively, regardless of calibration compliance (Figure 5). Additionally, LP_{Irad} was significantly greater with medium calibration compliance (compared to low calibration compliance), for all levels of estimation compliance except perfect (Figure 4). This difference occurred because both calibration steps (low and medium calibration compliance) were constrained to the same RCT result; if calibration compliance decreases, the pathogen concentrations must also decrease for the model to remain consistent with the Lifestraw RCT. During the estimation step, the higher LP_{Prad} for medium calibration compliance is due to lack of protection from the perfect placebo; as a result, the LP_{Irad} values were also higher. The differences between low and medium calibration compliance decrease as estimation compliance increases.

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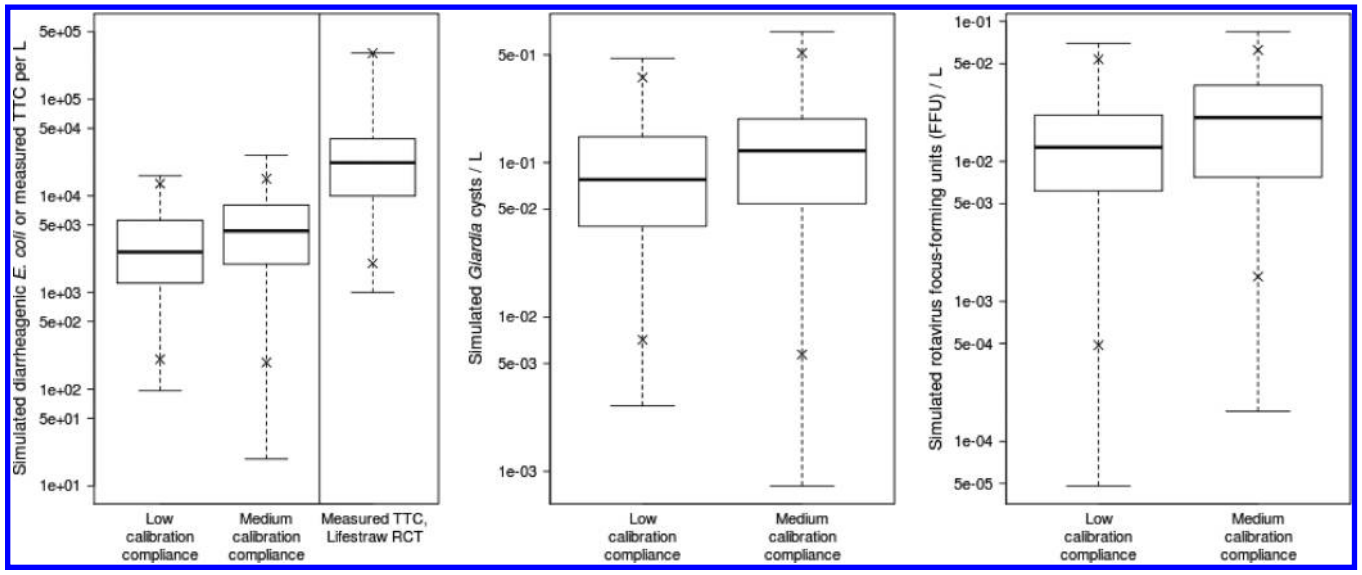

Figure 3. Simulated distributions of microbial concentrations per liter of untreated water, consistent with the Lifestraw RCT. Distributions were obtained from the calibration step assuming low (65% of children treat $^1/_3$ of their drinking water) or medium (65% of children treat $^2/_3$ of their drinking water) calibration compliance. Thermotolerant coliforms (TTC) measured by the Lifestraw RCT are also shown for comparison with simulated *E. coli*. For all three pathogen types, the concentration distributions differ by calibration compliance (Wilcoxon rank sum test, $p < 0.001$).

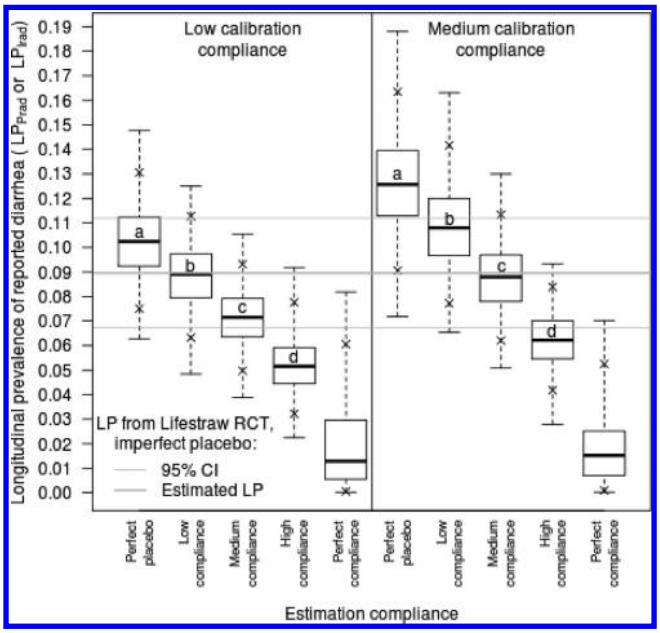

Figure 4. Distributions of reported longitudinal prevalence (LP) of diarrhea in the estimation step for the intervention group, by calibration compliance and estimation compliance. a, b, c, d: Each of these pairs of distributions differed significantly by calibration compliance (Wilcoxon rank sum test, $p < 2 \times 10^{-16}$). Compliance levels: Perfect placebo (100% of children treat 0% of their drinking water), low compliance (65% of children treat $^1/_3$ of their drinking water), medium compliance (65% of children treat $^2/_3$ of their drinking water), high compliance (65% of children treat 100% of their drinking water), perfect compliance (100% of children treat 100% of their drinking water).

Calibration compliance altered the estimated effect of a perfect placebo (Figure 5). Adjustment for the imperfect placebo increased the estimated preventable fraction of disease by 8 percentage points assuming low calibration compliance (median LPR_{rad}: 0.94 and 0.86 for imperfect and perfect placebo, respectively). Assuming medium calibration compliance, the preventable fraction increased by 22 percentage points (median LPR_{rad}: 0.92 and 0.70 for imperfect and perfect placebo, respectively).

All three pathogen types contributed substantially to infection and disease (SI, Figure S5). Multiple infections accounted for about 2% of infections.

DISCUSSION

Results from an epidemiological study may only be relevant to the ecological and social conditions of the communities studied. However, quantitative microbial risk assessment (QMRA) models that are calibrated to epidemiologic data can predict risk under scenarios that were not actually studied, known as counterfactual scenarios.[28,29] This calibration process can enhance QMRA models that are usually informed by environmental contamination data under conditions where direct risks are difficult to measure using epidemiology. There are many situations where epidemiological data can be used to inform QMRA models, such as in a developing country context where direct measures of risk are frequently measured but environmental contamination data are rare. We applied our modeling framework in this context to generalize results from the Lifestraw RCT.[12]

Generalizing across different compliance scenarios, we used our model to quantify the relationship between compliance and HWT effectiveness. Our analysis suggests that perfect compliance in the Lifestraw RCT communities would yield an LPR_{rad} of 0.13, suggesting that 87% of reported diarrhea could be prevented by consumption of treated water. This result, suggesting that only 13% of diarrhea in the Lifestraw RCT community was caused by nonwaterborne transmission, is consistent with a HWT trial in a refugee camp in which there was 95% compliance and an 83% reduction in diarrhea prevalence,[30] as well as numerous field trials of ceramic filters indicating risk ratios <0.5.[8,31] Lower compliance will result in an underestimate of protective effect compared to a situation in which there is better compliance. Additionally, these trials and our risk assessment model do not account for the

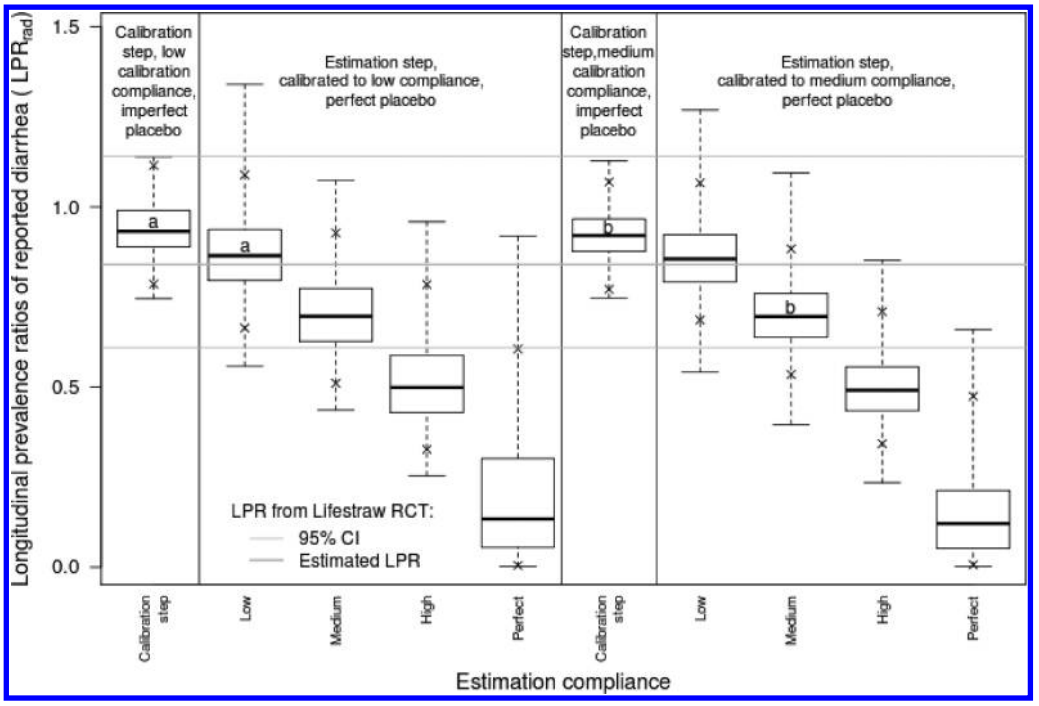

Figure 5. Distributions of longitudinal prevalence ratios for reported diarrhea (LPR_{rad}) in the estimation step for the intervention group, by calibration compliance, estimation compliance, and placebo type. a, b: These pairs of distributions illustrate the effect of the imperfect placebo on LPR_{rad}, depending on low (a) or medium (b) calibration compliance. They differed significantly by imperfect vs perfect placebo (Wilcoxon rank sum test, $p < 2 \times 10^{-16}$).

interdependency of other transmission routes. Thus, we cannot be certain that this model accurately assesses the proportion of diarrhea associated with drinking water.

The reduction in effectiveness due to the imperfect placebo also depended on the assumed calibration compliance level during the Lifestraw RCT. Assuming low calibration compliance, the imperfect placebo decreased effectiveness (preventable fraction) by 8 percentage points. Effectiveness decreased 22 percentage points assuming medium calibration compliance (Figure 5).

Compliance has several components. Our analysis uses a simple formulation in which each child has a daily probability of using the device; if the device is used, a fixed proportion of water is treated. In reality, some people may be highly consistent users or nonusers, while others might use the device occasionally (e.g., drinking untreated water while working outside the home). Effectiveness might differ given perfect use by 50% of a population, compared to an entire population treating 50% of their water; however, these distinctions are better suited to a more advanced model (e.g., a transmission model incorporating feedback loops) than the linear QMRA model described here.

These results are consistent with the reasonable expectation that increasing compliance should increase effectiveness. Recent systematic reviews suggest a positive but not statistically significant relationship between compliance and effectiveness, perhaps due to difficulty in measuring compliance.[7,8,10] Modeling has shown how even occasional treatment failures by a water treatment plant could cause high levels of diarrheal disease in populations.[32] Collectively, these results show the importance of consistent treatment of drinking water, by well-managed municipal plants or by high compliance with HWT. Future studies should examine the joint effects of compliance and $\log_{10}$ removals by a HWT device. QMRA models can be used to extend the results shown in Figure 5 by providing estimates for risk reductions as a function of both compliance and device efficacy. For example, for a given compliance level, what are the expected risk reductions when using a device that provides 4 $\log_{10}$ removal, versus a device that provides 3 $\log_{10}$ removal? Such analyses could provide performance metrics and standards that address not only microbiological efficacy but also the correct, consistent, and sustained use of a device by the target population.

Predicting Pathogen Concentrations in Drinking Water Sources. Few data exist on pathogen concentrations that individuals ingest via drinking water in developing countries. The calibration step of this model used the epidemiological data from the Lifestraw RCT to predict concentrations of pathogens in untreated water. The predicted *Giardia* concentrations are consistent with measurements from southeastern Brazilian raw water sources (<0.1 to 3.4 cysts/L),[33] but lower than other Brazilian (2.5−120 cysts/L)[34] or Honduran source waters (2.4−21 cysts/L).[35] The predicted diarrheagenic *E. coli* concentrations are much lower than the 2.5×10^5 to 1.6×10^7 CFU of enterotoxigenic *E. coli* detected in sewage-impacted Indian rivers.[36] Furthermore, the predicted rotavirus concentrations are substantially lower than measurements from polluted creeks in Sao Paulo, Brazil (geometric mean, ~2.7 focus-forming units/L).[37] It is reasonable that the clear source water in the Lifestraw RCT would have lower pathogen concentrations than the above water sources, many of which were from polluted urbanized environments.

Accounting for viable pathogen concentrations in drinking water (and other exposure routes) in epidemiological studies would increase the accuracy and precision of risk estimates, because indicators of fecal contamination (e.g., coliform bacteria or *E. coli*) correlate poorly with presence or concentrations of actual pathogens.[38−40]

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Calibration of Microbial Risk Assessment Models. Microbial risk models, like many environmental models, can never be fully validated.[41] However, they can be confirmed through a calibration process using epidemiological data. We present a framework that first calibrates the model using epidemiological data, and second uses the model to estimate risk under differing counterfactual scenarios. The calibration process transforms uninformed priors to informed posteriors by constraining the model using the epidemiological outcome data from the Lifestraw RCT. The low percentage of simulation runs that were consistent (<0.3%) with epidemiological data indicate that the trial data imparted substantial information to the model by constraining the acceptable parameter space. Source water pathogen data would be useful to further calibrate the model for the Congo field site.

Risk models informed by epidemiological data are powerful tools to generalize beyond the context in which epidemiological studies are conducted. Models can be used to inform study design and intervention strategies; epidemiological studies can calibrate these models. Few published examples take this approach (but see refs 28, 29). The framework provided here can facilitate such future research activities. Results from our examination of HWT field trials indicate that compliance and pathogen concentrations in source water are particularly important processes to characterize. Data from these processes would enhance the calibration step, providing the opportunity to describe other unobserved aspects of the system. Additionally, pathogen measurements from other environmental sources (e.g., hands, food, feces) would facilitate the extension of our model system to consider transmission by multiple environmental pathways;[42] such transmission models would allow investigation of interdependency of multiple transmission routes, and ultimately multiple antidiarrheal interventions.

Although additional data on pathogen concentration and compliance, as well as more advanced transmission models, are important steps forward in informing intervention strategies, our analysis provides the important and robust conclusion that effectiveness is highly sensitive to compliance, suggesting that trials of household level interventions should measure compliance as carefully and as effectively as possible. Compliance guidelines should be developed for HWT interventions, in addition to the microbial reduction guidelines for HWT devices recently published by WHO.[43]

■ ASSOCIATED CONTENT

Supporting Information

Explanation of implementation of each distinct simulation run and the reasoning behind the design and assumptions of the model; additional figures and table; source code for the model. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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