Estimating infection risks and the global burden of diarrheal disease attributable to intermittent water supply using QMRA

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ABSTRACT

Intermittent water supply (IWS) is prevalent throughout low and middle-income countries. IWS is associated with increased microbial contamination and potentially elevated risk of waterborne illness. We used existing datasets to estimate the population exposed to IWS, assess the probability of infection using quantitative microbial risk assessment, and calculate the subsequent burden of diarrheal disease attributable to consuming fecally contaminated tap water from an IWS. We used reference pathogens *Campylobacter*, *Cryptosporidium*, and rotavirus as conservative risk proxies for infections via bacteria, protozoa, and viruses, respectively. Results indicate that the median daily risk of infection is an estimated 1 in 23,500 for *Campylobacter*, 1 in 5,050,000 for *Cryptosporidium*, and 1 in 118,000 for rotavirus. Based on these risks, IWS may account for 17.2 million infections causing 4.52 million cases of diarrhea, 109,000 diarrheal DALYs, and 1,560 deaths each year. The burden of diarrheal disease associated with IWS likely exceeds the WHO health-based normative guideline for drinking water of 10^{-6} DALYs per

person per year. Our results underscore the importance water safety management in water supplies and the potential benefits of point-of-use treatment to mitigate risks.

INTRODUCTION

An intermittent water supply (IWS) is a piped water supply that delivers water to end-users on a discontinuous basis, with days or hours of interruption, due to operational constraints including inadequate access to water and energy, distribution system deficiencies, pipe breakages, poor governance or other issues *(1)*. IWS is prevalent in many low and middle-income countries (LMICs) *(2)*. From 2004 to 2013, the International Benchmarking Network (IBNET), documented water supply lasting less than 24 hours per day in 44 of the 102 countries included in the database *(3)*. In 2000 the World Health Organization (WHO) estimated that 60% of the population served by piped water in Latin America and the Caribbean were served by IWS *(4)* and that at least one in three urban water supplies in Africa and one in two in Asia operated intermittently *(5)*. The rapid development of piped water supplies in LMICs, especially in rural and peri-urban areas *(6)*, climate change *(7)*, and urbanization, together exert increasing pressure on the resources required to maintain piped water supply functionality, and suggests that the population served by IWS could increase significantly in the coming years.

Users of IWS are exposed to increased health risks because such supplies are subject to increased microbial contamination *(8)* through the intrusion of environmental water from outside the pipeline during low-pressure events, microbial regrowth during stagnant periods, biofilm scouring during re-pressurization, and household storage in response to unreliable supply *(2, 9)*. As summarized in Table S1, the available evidence suggests large variability in the prevalence of fecal contamination in IWS

networks with the proportion of samples positive for fecal coliforms ranging from 4% to 76% and *E. coli* from 2% to 32%. Quantitative studies of fecal indicators also suggest high variability in measures of central tendency and counts ranging over several orders of magnitude: *E. coli* from 0.5 MPN/100 mL to 520 CFU/100 mL and fecal coliform from 4 CFU/100 mL to 175 CFU/100 mL (Figure S1). In the only study documenting *E. coli* counts in an IWS compared with a continuous water supply (CWS), 31.7% of samples in the IWS were positive for *E. coli* while only 0.7% of samples were positive for *E. coli* in the CWS *(10)*. A majority of studies documenting microbial contamination in IWS networks are cross-sectional and of small sample size and therefore fail to adequately document the temporal variability of microbial water quality in an IWS. Nonetheless, the best available data indicate that fecal contamination is frequently detected in IWS tap water and that contamination prevalence is likely to be much greater in an IWS compared to a CWS.

Maintenance of adequate disinfectant residual is essential to reduce the risks of contamination during distribution. Low disinfectant residuals are often observed LMICs *(11)*, however, potentially increasing risks associated with IWS. Fecal contamination in an IWS has been associated with epidemics of typhoid in Tajikistan *(12)* and cholera in Peru *(13)*. However, endemic gastrointestinal illness (GII) associated with IWS has proven harder to detect. In a meta-analysis, Ercumen et al. *(14)* concluded that users of IWS had 1.61 times greater odds of GII compared to those that were served by a CWS (OR=1.61, 95% CI: 1.26-2.07). More recent studies of IWS and GII have yielded mixed results, with one finding no association between IWS and diarrhea *(15)* and another finding an association between cholera incidence and supply intermittency *(16)*. The current epidemiological evidence, summarized in Table S2, suggests that intermittent supply has been associated with epidemic transmission of waterborne diseases such as cholera and typhoid, but statistically meaningful associations between IWS and endemic GII are more difficult to establish.

Given the global prevalence of IWS, the observed fecal contamination in such supplies, and the absence of clear epidemiological evidence concerning the endemic health risks associated with IWS, quantitative microbial risk assessment (QMRA) offers a potentially useful tool for characterizing the risk of infection for

fecal-oral pathogens associated with IWS and the attributable burden of diarrheal disease *(17)*. QMRA can make use of relevant microbiological datasets alongside mathematical models to estimate the health effects of human exposures to pathogens *(18)*. QMRA has been used to estimate the health risks associated with drinking water for a number of waterborne pathogens including viruses *(19)*, bacteria *(20)*, and protozoa *(21)*, and for a variety of exposure scenarios, including intrusion of groundwater, surface water, and sewage *(22)*. The application of QMRA in LMICs has been limited by scarcity of the data required to populate models. However, QMRA approaches have been used to estimate public health risks attributable to piped water supplies in Kampala, Uganda *(23)* and Accra, Ghana *(24)*. Such studies demonstrate the viability of the approach and its importance in risk management in resource limited settings such as those where IWS is prevalent. In this paper, we use QMRA to estimate the global burden of infection, morbidity, and mortality associated with IWS.

MATERIALS AND METHODS

We used Monte Carlo techniques to estimate the risks of infection associated with human exposures to three reference pathogens (*Campylobacter*, *Cryptosporidium*, and rotavirus) through the consumption of fecally contaminated tap water delivered by an IWS. We made use of three existing datasets: *E. coli* measurements in IWS tap water samples, measured pathogen to *E. coli* ratios in sewage, and published dose-response models to estimate the risk of infection. We fit probability distributions to each input dataset and executed Monte Carlo simulations in Oracle Crystal Ball software *(25)*. We then used the predicted median annual risk of infection for each reference pathogen and an estimate of the number of IWS users to quantify a global burden of diarrheal disease, including disability adjusted life years (DALYs) and deaths, associated with IWS. This manuscript is organized using the conventional QMRA framework consisting of hazard identification, exposure assessment, dose-response and risk characterization *(26)*. The framework for the risk assessment model as we implemented it is illustrated in Figure 1.

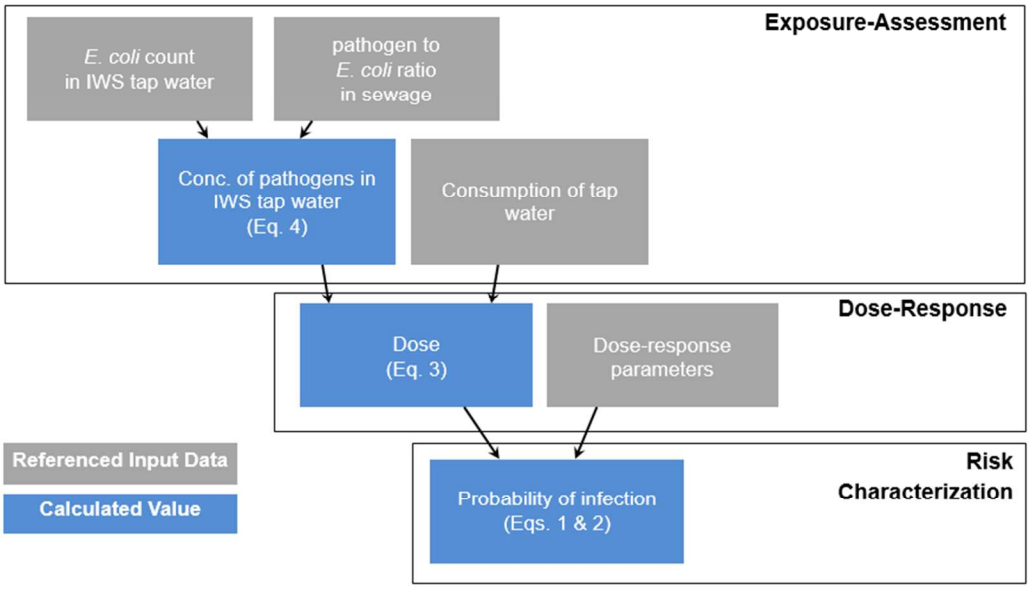

Figure 1| A schematic of the Monte Carlo framework used to estimate the daily probability of infection for *Campylobacter*, *Cryptosporidium*, and rotavirus assuming the consumption of fecally contaminated tap water from an IWS.

Hazard Identification

In the absence of published measurements of waterborne pathogens in an IWS, we utilized a reference pathogen approach *(27)*. We selected *Campylobacter jejuni*, *Cryptosporidium parvum*, and rotavirus as reference pathogens, following the model development guidance articulated in the WHO *Guidelines for Drinking-water Quality* (GDWQ) and supporting documentation *(27-30)*. While these reference pathogens may not represent the greatest microbial drinking water exposure risks globally, they can be used as conservative proxies for each of the major waterborne pathogen classes in risk estimation. They also have well-characterized dose-response relationships, moderate to long persistence in water supplies, high infectivity, and moderate to high resistance to chlorine, making them suitable as proxies in risk estimation for waterborne pathogens *(27)*.

Campylobacter is a pathogenic bacterium that has caused disease outbreaks associated with contaminated drinking water supplies *(31, 32)*. It has a low infectious dose *(33)* with symptoms including diarrhea, fever, nausea, and vomiting, with rare sequelae (Guillain-Barré syndrome) *(34)*.

Cryptosporidium is a protozoan parasite that has caused large outbreaks of disease through transmission in piped water supplies *(35)*. The infectious dose of *Cryptosporidium* has been estimated to be as low as 1 to 10 oocysts *(36)* with most infections leading to acute diarrhea, with increased risks of serious illness and death among immunocompromised individuals *(34)*. Although commonly associated with hygiene-related transmission, rotavirus has caused significant waterborne disease outbreaks in Rio de Janeiro *(37)*, Colorado *(38)*, and China *(39)*. One rotavirus particle is capable of initiating an infection *(40)* leading to fever, vomiting, and acute diarrhea and, in low income settings, presents a significant risk of death among children *(34)*. The selection of *Campylobacter*, *Cryptosporidium*, and rotavirus as reference pathogens is supported by findings from the Global Enteric Multicenter (GEMS) Study *(41, 42)* and a multisite birth cohort study (MAL-ED) *(43)* that identified each of them as important etiological agents of moderate-to-severe cases of diarrhea among children under 5 in LMICs.

Dose-Response

The probability of infection following ingestion of a dose of *Campylobacter* or rotavirus is best fit by a Beta-Poisson function *(33, 44, 40)*, Equation 1, characterized by the median infectious dose, N_{50}, the Beta distribution parameter alpha, α, and the dose, d. Probability of infection for ingesting *Cryptosporidium* is best characterized by an exponential dose-response function *(45)*, Equation 2, described by parameters k, and the ingested dose, d. For each reference pathogen, we used the dose response parameters from previously published dose-response fittings and modeled them using lognormal probability density functions (PDF) as described in Table 1 *(46)*.

$$P_{inf}(d) = 1 - \left[1 + \frac{d}{N_{50}}\left(2^{\frac{1}{\alpha}} - 1\right)\right]^{-\alpha} \quad (1)$$

$$P_{inf}(d) = 1 - e^{(-k*d)} \quad (2)$$

Exposure Assessment

In an IWS, periods of low-pressure allow contamination from sewage, groundwater, surface water, or other environmental waters to intrude into the pipelines through holes and cracks *(47)*. When the system

is re-pressurized to deliver water to consumers, contaminated water is transported to the taps where it is either used upon delivery or stored for later use. Due to a lack of robust datasets on water quality following household storage due to IWS, our analysis considers the risks of infection posed by IWS if the drinking water were consumed the moment it arrives at the tap (i.e., point-of-entry), without considering re-growth, inactivation, recontamination in storage via unsafe handling practices, or point-of-use water treatment and further storage *(48)*. Quantifying the dose of pathogen ingested at the moment of exposure as shown in Equation 3 is termed exposure assessment.

$$Dose\ (d) = C_{\ pathogen,\ IWS}\left(\frac{N}{mL}\right) * V_{water\ consumed,\ IWS}\ (mL) \quad (3)$$

We modeled water consumption in milliliters ($V_{water\ consumed,\ IWS}$) as a uniform PDF with a minimum of one thousand per day and maximum of two thousand per day based on the use of one liter per day in WHO risk estimates *(27)* and two liters per day for adult drinking water consumption in the United States *(49)*. To estimate the PDF for the concentration of each reference pathogen ($C_{pathogen,\ IWS}$), in the absence of direct measurements of pathogens in IWS tap water, we used a previously developed method of quantifying waterborne pathogens in water distribution networks using pathogen to *E. coli* or thermotolerant coliform ratios *(22, 50)*. In this approach, the number of pathogens per volume of drinking water is calculated by multiplying the concentration of *E. coli* measured in IWS tap water by the observed ratio of pathogen to *E. coli* in a potential source of fecal contamination, in this scenario sewage, as shown in Equation 4.

$$C_{pathogen,\ IWS}\left(\frac{N}{100mL}\right) = C_{E.\ coli,\ IWS}\ \left(\frac{N}{100\ mL}\right) * \left[\frac{C_{pathogen}\left(\frac{N}{100mL}\right)}{C_{E.\ coli}\left(\frac{N}{100mL}\right)}\right]_{raw\ sewage} \quad (4)$$

We developed a PDF of the *E. coli* count in IWS tap water using data from three studies of fecal contamination in IWS systems in three locations: Kandal Province, Cambodia *(51)*; Da Nang Province, Vietnam *(52)*; and Hubli-Dharwad, India *(10)*. These studies were selected because of their large sample

size and use of robust methods to quantify *E. coli*. We log transformed the *E. coli* counts and used maximum likelihood techniques to parameterize the normal distribution that maximized the likelihood of obtaining the observed values. For values below and above detection limits, we used the value of the cumulative normal distribution function to incorporate these censored measures into the maximum likelihood estimation (MLE) per previously described methods *(53)*. We estimated the log transformed *E. coli* counts to be normally distributed with mean of 0.17 and standard deviation of 1.57 as shown in Table 1. Boxplots of log *E. coli* counts from each study, the pooled dataset, and the MLE model (Figure S2) show that the quartiles, median, and mean of the underlying data compare well with the modeled distribution. The frequency and cumulative distributions (Figures S3 and S4) indicate that the MLE model of the *E. coli* count is comparable to the underlying field observed *E. coli* distributions.

For the second term of Equation 4, we developed PDFs of the ratio of each reference pathogen to *E. coli* in raw sewage using paired measurements from sewage. Paired measures from sewage sources specific to locations where IWS is prevalent could not be found in the literature, so we used observations from a sewage treatment plant in the Netherlands *(54)* (ratio of *Cryptosporidium* and enterovirus to thermotolerant coliforms) and German sewer systems *(55)* (ratio of *Campylobacter* to *E. coli*). Since robust measurements of thermotolerant coliform measurements in IWSs were unavailable in the literature, we assumed that 95% of thermotolerant coliforms in the measured ratios were *E. coli*. Additionally, we substituted rotavirus for enterovirus in the observed ratio. We used the previously described MLE technique on the log transformations of the observed ratios to parameterize the normal distribution that maximized the likelihood of observing the documented measures. The probability distributions and parameters for the reference pathogen to *E. coli* ratios in are summarized in Table 1.

Table 1| Descriptive statistics of the probability density functions used to model each stochastic parameter in the Monte Carlo simulation.

DOSE-RESPONSE PARAMETERS				
Pathogen	**Dose-Response Parameter**	**Distribution**	**Distribution Description**	**Reference**
Campylobacter	α N_{50}	Lognormal Lognormal	Mean: 1.51×10^{-1} Std. Dev.: 5.90×10^{-2} Mean: 1.69×10^{3} Std. Dev.: 2.78×10^{3}	*(33, 44)*
Cryptosporidium	k	Lognormal	Mean: 3.44×10^{-1} Std. Dev.: 2.02	*(45)*
rotavirus	α N_{50}	Lognormal Lognormal	Mean: 2.48×10^{-1} Std. Dev.: 1.46×10^{-1} Mean: 8.16 Std. Dev.: 6.65	*(40)*
EXPOSURE ASSESSMENT PARAMETERS				
Parameter		**Distribution**	**Distribution Description**	**Reference**
Tap Water Consumption		Uniform	Min: 1 L Max: 2 L	*(27, 49)*
Log *E. coli* count in IWS tap water		Normal	Mean: 0.17 Std. Dev.: 1.57	*(10, 51, 52)*
Campylobacter to *E. coli* ratio in sewage		Lognormal	Mean: 8.89×10^{-3} Std. Dev.: 1.33	*(55)*
Cryptosporidium to fecal coliform ratio in sewage		Lognormal	Mean: 1.13×10^{-6} Std. Dev.: 9.26×10^{-6}	*(54)*
Rotavirus to fecal coliform ratio in sewage		Lognormal	Mean: 8.79×10^{-7} Std. Dev.: 1.77×10^{-6}	*(54)*

Risk Characterization

To test the mathematical framework and plausibility of the proposed model, we first made point estimates of the daily and annual risk of infection, and the subsequent diarrheal burden of disease. After we reviewed the point estimates, we entered each stochastic variable using the PDFs as described and conducted Monte Carlo simulations in Crystal Ball. Each variable was drawn 10,000 times per the PDF that describes it and each individual input was propagated through the described equations to produce a distribution of the daily probability of infection. We estimated the median, mean, their associated confidence intervals, and percentiles of the probability of infection by bootstrapping the model with 200 samples of 1,000 trials each. We evaluated the sensitivity of the estimated risks of infection to changes in the input variables by means of tornado analysis and rank correlation. In the tornado analysis, we varied each input from its 10^{th} to 90^{th} percentile and measured the associated variability in the predicted risk of infection while holding all other inputs constant. Rank correlation was determined using Spearman's rank correlation between each input variable and the predicted risk of infection.

Population served by IWS Estimate

We made a robust estimate of the population served by IWS by projecting the IBNET reported prevalence of intermittent service onto JMP measures of access to piped-on-premise water supplies *(56)*. The IBNET database contains more than 22,000 records from 119 countries dating from 1995 to 2014 *(57)*. Each record consists of a single utility's self-reported performance data for a single year. For this analysis, we used only the most recent record from any single utility that contained both the number of hours the utility supplied water per day and the number of people it supplied. To exclude supply interruptions for repairs and maintenance associated with normal operations in a CWS, we defined an IWS as a utility reporting less than an average of 23 hours per day of service. We further limited our analysis to utilities reporting from countries defined as LMICs by the World Bank. After we removed records that were incomplete, outdated, or from high income countries, 2,591 records pertaining to utilities serving over 773 million people in 91 LMICs were included in the analysis (Figure S5). After screening, we stratified utilities reporting IWS into WHO regions and calculated an average percentage of utilities in that region that were such. We then bootstrapped this average percentage using 10,000 iterations to estimate 95% confidence intervals for each region. We then calculated the average and 95% confidence interval for the global estimate similarly. To calculate the magnitude or persons served by IWS for each WHO region and globally, we multiplied the estimated percentages and confidence intervals by the number of persons receiving their drinking water from a piped-on-premise supply for each WHO region per the 2015 JMP Update.

Burden of Disease Calculations

We combined the probabilities of infection for each reference pathogen with the estimated number of IWS users by region to calculate the total number of infections, cases of diarrhea, diarrheal disability-adjusted life years (DALYs), and deaths attributable to the consumption of fecally contaminated tap water from an IWS. Following previously articulated methods, it was assumed that the probability of a case of diarrheal illness given infection with *Campylobacter* was 30% with 100% of the population susceptible, *Cryptosporidium* was 70% with 100% of the population susceptible, and rotavirus was 50% with 13% of the population susceptible *(27, 58)*. The DALY weighting used in the burden of disease calculations for

Campylobacter was 4.6 x 10^{-3} DALYs per case, *Cryptosporidium* was 1.47 x 10^{-3} DALYs per case, and for rotavirus in low-income countries was 0.482 DALYs per case *(58)*. We calculated deaths attributable to infection with each reference pathogen assuming probability of mortality for *Cryptosporidium* of 10^{-5} per case of diarrhea, probability of mortality due to gastroenteritis associated with *Campylobacter* of 10^{-4} per case of diarrhea and probability of mortality associated with rotavirus of 0.6% per case of diarrheal illness *(58)*. We also assumed that 2.3% of *Campylobacter* cases develop Guillain-Barré syndrome with an associated probability of mortality of 2 x 10^{-4} *(58)*. We compared the estimated annual burdens of diarrheal disease to the level of acceptable risk from drinking water of 10^{-6} DALYs per person per year as proposed by the WHO *(27)*. This threshold represents an excess risk of 1 in 100,000 and equates to everyone experiencing one mild self-limiting case of diarrhea every 10 years due to the consumption of unsafe water.

RESULTS AND DISCUSSION

Point Estimates of Infection Risks

We made point estimates of the daily and annual risk of infection, and the annual burden of diarrheal disease, for each reference pathogen using median values of the observed *E. coli* concentration in IWS tap water (1.3 CFU/100 mL) along with median values of the ratio of reference pathogen to *E. coli* in sewage, tap water consumption, and dose-response parameters. These point estimates indicate that, of the pathogens considered, *Campylobacter* poses the greatest risk of infection, possibly due to the greater ratio of *Campylobacter* to *E. coli* observed in sewage from Germany *(55)*. At the median *E. coli* value in IWS tap water, the annual burden of diarrheal disease for *Campylobacte*r and rotavirus both exceed the WHO threshold value of 10^{-6} DALYs per person per year (Table S3). When the mean *E. coli* concentration observed in IWS tap water is used, the annual burden of diarrheal disease for each reference pathogen exceeds this threshold (Table S4). For comparison, point estimates of infection risks and burden of diarrheal disease were also calculated for each pathogen using pathogen to *E. coli* ratios in untreated wastewater as documented in the Table 7.6 of the GDWQ *(27)*. As shown in Table S5, the ranking of pathogens by risk of infection remains consistent between the GDWQ pathogen to *E. coli* ratios and the pathogen to *E. coli* ratios used in the model.

Monte Carlo Estimates of Infection Risks

The median daily probabilities of infection predicted by the Monte Carlo simulations, summarized in Table 2, are consistent with the point estimates with the highest risk associated with *Campylobacter* (4.26×10^{-5} 95% CI: 1.92×10^{-5} – 7.89×10^{-5}) followed by rotavirus (8.47×10^{-6} 95% CI: 3.77×10^{-6} – 1.77×10^{-5}) and *Cryptosporidium* (1.98×10^{-7} 95% CI: 8.31×10^{-8} – 3.71×10^{-7}). These translate to median annual probabilities of infection of 1.54% for *Campylobacter*, 0.309% for rotavirus, and 0.007% for *Cryptosporidium*. The upper bounds of the daily probability of infection, as defined by the 90th percentile and shown in Table 2, were 25% for *Campylobacter*, 0.34% for *Cryptosporidium*, and 7.3% for rotavirus. The cumulative distributions of the daily probability of infection for each reference pathogen, shown in Figures S6, S7, and S8, illustrate that the mean daily risk of infection for each reference pathogen was greater than the 80th percentile. For this reason, we used the median risks of infection and their associated confidence intervals to make a conservative calculation of the diarrheal burden of disease associated with the consumption of fecally contaminated tap water delivered by an IWS.

Table 2 | Median, 10th percentile, and 90th percentile daily probabilities of infection for each reference pathogen assuming consumption of fecally contaminated tap water from an IWS as estimated using Monte Carlo simulation.

Pathogen	10th Percentile Daily $P_{infection}$	Median Daily $P_{infection}$	90th Percentile Daily $P_{infection}$
Campylobacter	2.11×10^{-12}	4.26×10^{-5} 95% CI: 1.92×10^{-5} – 7.89×10^{-5}	2.50×10^{-1}
Cryptosporidium	1.21×10^{-14}	1.98×10^{-7} 95% CI: 8.31×10^{-8} – 3.71×10^{-7}	3.43×10^{-3}
rotavirus	5.62×10^{-13}	8.47×10^{-6} 95% CI: 3.77×10^{-6} – 1.77×10^{-5}	7.32×10^{-2}

Model Sensitivity

For *Cryptosporidium* and rotavirus, most of the variation in the predicted risk of infection was explained by the *E. coli* count in IWS tap water (*Cryptosporidium*: 45.86%; rotavirus: 81.42%) followed by the pathogen to *E. co*li ratio (*Cryptosporidium*: 32.75%; rotavirus 9.79%). For *Campylobacter*, the opposite was observed with 85.44% of the variation explained by the *Campylobacter* to *E. coli* ratio followed by the *E.*

coli count in IWS tap water with 8.52%. The dose response parameters for each pathogen explained most of the remaining uncertainty followed by the tap water consumption variable. The sensitivity analysis summarized in Tables S6, S7, and S8, highlights the importance of the *E. coli* counts in IWS tap water and the ratio of the reference pathogens to *E. coli* in estimating the risk of infection in the current assessment.

Global Population served by IWS

Our preliminary estimate of the IWS population based on WHO reports and the 2015 JMP data and summarized in Table S9, found that approximately 1 billion people were likely exposed to IWS. The results of our more robust estimate made using IBNET and JMP data, listed in Table S10, indicate that the global population served by IWS is 925 million (95% CI: 670 – 1,130 million) with almost half (44.2%) of those exposed living in South-east Asia and a significant number living in India (Figure S9).

Diarrheal Burden of Disease Calculations

Given the estimated population served by IWS and the median annual infection risk, the reference pathogens together account for 17.2 million (95% CI: 7.76 – 32.3) infections annually among IWS users. Of these infections, 83% are attributable to *Campylobacter*, 17% to rotavirus, and less than 1% to *Cryptosporidium*. These infections cause 4.52 million (95% CI: 2.04 – 8.36) cases of diarrhea annually with *Campylobacter* accounting for 95% of these cases while *Cryptosporidium* and rotavirus account for 1% and 4% each. These cases of diarrhea cause 109,000 DALYs (95% CI: 48,800 – 223,000) and 1,560 deaths (95% CI: 699 – 3,150) per year. Burden of disease estimates based on the median infection risks are summarized by WHO region in Table 3. Rotavirus accounts for 82.1% of annual diarrheal DALYs and deaths, while *Campylobacter* accounts for 18.1% of DALYs and deaths. In this exposure scenario, *Cryptosporidium* accounts for less than 1% of both annual DALYs and deaths among users of IWS. The burden of disease stratified by etiology is tabulated in Table S11. The predominance of rotavirus in the annual diarrheal disease burden is driven by its high DALY weighting in LIMCs (0.482 per case) along with its high LMIC case fatality rate (0.6%). *Campylobacter*'s burden of disease is driven by its high risk of infection, one order of magnitude greater than rotavirus, and population susceptibility of 100%. While it is

also assumed that 100% of the population is susceptible to diarrheal disease from *Cryptosporidium* infection, the median infection risk for the organism is two orders of magnitude less than that of *Campylobacter*.

Table 3 | Annual infections, diarrheal cases, DALYs, and deaths attributable to IWS as calculated using the median daily probability of infection and its associated 95% confidence interval for *Campylobacter*, *Cryptosporidium*, and rotavirus assuming consumption of fecally contaminated tap water from an IWS.

Region	Population served by IWS (Millions)	Annual Infections (Millions)	Annual Diarrheal Cases (Millions)	Annual Deaths	Annual DALYs (Thousands)
Africa	116	2.16 95% CI: 0.973 – 4.06	0.566 95% CI: 0.256 – 1.05	196 95% CI: 88 – 395	13.7 95% CI: 6.12 – 28.0
Americas, LMI	47.0	0.874 95% CI: 0.394 – 1.64	0.229 95% CI: 0.104 – 0.424	79 95% CI: 36 – 160	5.55 95% CI: 2.48 – 11.3
Eastern Mediterranean, LMI	103	1.91 95% CI: 0.864 – 3.60	0.503 95% CI: 0.227 – 0.930	174 95% CI: 78 – 351	12.2 95% CI: 5.43 – 24.8
Europe, LMI	71.0	1.32 95% CI: 0.596 – 2.48	0.346 95% CI: 0.157 – 0.641	120 95% CI: 54 – 242	8.38 95% CI: 3.75 – 17.1
South-East Asia	409	7.60 95% CI: 3.43 – 14.3	2.00 95% CI: 0.902 – 3.69	691 95% CI: 309 – 1,390	48.3 95% CI: 21.6 – 98.6
Western Pacific, LMI	179	3.33 95% CI: 1.50 – 6.26	0.874 95% CI: 0.395 – 1.62	302 95% CI: 135 – 609	21.1 95% CI: 9.44 – 43.2
Global	**925**	**17.2** **95% CI: 7.76 – 32.3**	**4.52** **95% CI: 2.04 – 8.36**	**1,560** **95% CI: 699 – 3,150**	**109** **95% CI: 48.8 – 223**

The cumulative distributions of the annual burden of diarrheal disease for each reference pathogen, shown in Figures S6, S7, and S8, indicate that the annual burden for *Campylobacter* exceeds the WHO health threshold (10^{-6} DALYs/person-year) at the 39th percentile, *Cryptosporidium* at the 62nd percentile, and rotavirus at the 33rd percentile. The cumulative distributions of total diarrheal DALYs and deaths among the 925 million global users of IWS, shown in Figure S10, indicate that the upper bounds, as defined by the 90th percentile, are 30.9 million diarrheal DALYs and 394,000 deaths.

Uncertainties and Limitations

As with all QMRA approaches, there are uncertainties and limitations in the input variables that should be accounted for when interpreting the results. A significant source of uncertainty for our risk is the absence of direct measurements of pathogen concentrations in IWS distribution networks. Without these measurements, across settings and time, we relied on estimated concentrations of reference pathogens by proxy using fecal indicator bacteria measurements and ratios of pathogens to indicators in possible sources of contamination. Concerning fecal indicator bacteria, we were only able to pool data from three high-quality studies conducted in India, Cambodia, and Vietnam. These studies represent a small portion of the geographical range of IWS, globally, and include no data from South America and sub-Saharan Africa. The *E. coli* datasets used in this analysis also do not include first flush data when fecal indicator concentrations may be much higher *(8)*. Further, the pooled dataset consists of *E. coli* measurements from both urban and rural supplies, which prevents stratifying infection risk by urban and rural location, a potential risk factor for contamination in piped water supplies *(59)*. Together, these two uncertainties prevent us from examining the variation in risk across geographic and human settlement location and we are confined to providing an estimate of risk across all IWS users.

Concerning ratios of pathogens to indicators in potential sources of contamination, the correlation between pathogens and indicators in any medium have proven highly variable *(60)*. In raw sewage, the concentration of indicator bacteria is fairly constant whereas the concentration of pathogens varies as a function of the infection prevalence in the contributing population *(61, 62)*. Thus, it is important to characterize the ratio using a distribution to capture this variability. There are few published datasets of pathogen to *E. coli* ratios in sewage particularly in LMICs; in this study, we derived ratios using datasets from the Netherlands and Germany. These datasets likely underestimate the pathogen loadings in sewage in LMICs where higher prevalence of diarrheal infection could result in increased pathogen concentrations relative to indicators in sewage *(63)*. For example, the mean ratio of norovirus GII to *E. coli* measured in wastewater drains and wastewater-impacted streams was around 6.3×10^{-4} in Accra, Ghana *(64)*, which is several orders of magnitude higher than the ratio assumed for rotavirus in this study. The pathogen to *E. coli* ratios used in this study likely lead to risk estimates that are conservative.

Sources of uncertainty can also be found in the assumptions underlying exposure assessment. First, in the absence of untreated tap water consumption data from LMIC settings, we modeled daily tap water consumption as a uniform distribution from 1 to 2 liters based on exposure scenarios articulated in EPA and WHO estimates *(27, 49)*. This probability distribution is not likely to be representative of water consumption behavior in settings where supplies are deficient and consumer behaviors include a complex system of household water management *(48)*. Second, the scenario being modeled is the consumption of drinking water as it is delivered to the tap. This behavior is unlikely in an IWS where users, who are accustomed to supply interruptions, may obtain water from multiple sources and often store water in tanks, cisterns, and other containers for hours to days before the water is used. Household water handling and storage involve several risk factors for contamination, such as unsafe storage and access; including these behaviors in the model would likely increase the estimated risks of infection *(65, 66)*. On the other hand, some households with IWS may employ point-of-use water treatment systems, which mitigate the risks posed by contamination if operated correctly and consistently over time. High-quality datasets of *E. coli* measurements in household storage facilities and household water treatment behavior in an IWS remain limited *(10)* and make accounting for such variables in a risk framework difficult. It should be noted that this risk assessment does not include scenarios beyond daily consumption of drinking water. Therefore, the estimated risks of infection and subsequent burden of disease calculations do not include infection and disease from water quantity related behaviors such as food and hand washing or the use of water for household hygiene, which are likely modulated by the water scarcity associated with IWS.

Further uncertainty is introduced to the risk assessment by the population-specific dose-response functions for the reference pathogens used in the model. The dose-response data for each of the reference pathogens were collected in human feeding studies conducted in high-income settings with healthy, and generally, for rotavirus, male, adults. These dose-response functions may underestimate the risk of infection for persons living in LMICs, including children under five who suffer disproportionately from enteric disease, and attendant risks associated with non-diarrheal effects of exposure *(41)* including the range of effects potentially associated with environmental enteric dysfunction (EED) and its potential

downstream impacts *(67)*. For each reference pathogen, the only disease endpoint considered was diarrhea, which neglects other, potentially more severe health outcomes such as stunting and chronic undernutrition related to EED *(68)*. These dose-response functions also do not consider the risk of infection among people living in LMICs who may be more susceptible to infections due to compromised immune status or who, conversely, may benefit from acquired immunity due to endemic exposure. Additionally, dose-response models do not yet take into account the effects of co-infection, which is prevalent in LMIC settings and may lead to increased risks of infection and longer-term sequelae. The risks associated with unsafe water are co-distributed in populations that are also at risk of undernutrition, high prevalence of co-infections, and other risk factors that would tend to exacerbate the effects of waterborne pathogen exposure. Risk estimates do not consider the elevated risks likely for infants, children, the undernourished, the immunocompromised, and those who are unlikely to receive timely treatment for diarrheal disease (e.g. oral rehydration therapy), which can dramatically reduce the risk of mortality among children in particular *(69)*.

Besides the previously mentioned limitations in estimating the risks of infection, further sources of uncertainty in the burden of disease calculations include both the estimates of the IWS population and the diarrheal disease weighting metrics. In regard to the population exposed to IWS, the JMP piped-on-premise measures do not include those who receive water from standpipes served by distribution systems. Additionally, the IBNET database relies on self-reported data from utilities that are mostly located in urban areas. Taken together, our estimates using these assumptions likely underestimate the population exposed to IWS. For the diarrheal disease per-case burden, the use of rotavirus per-case DALY weighting for LMICs instead of that for high-income countries increases the overall burden of disease and means the rotavirus burden has an outsized effect on the overall burden estimates. For instance, in LMICs, the rotavirus DALY weighting is 0.482 per case with a case fatality rate of 0.6%; in high-income countries, the recommended DALY weighting is only 0.0142 per case and the case fatality rate is 0.015% *(58)*. We have presented the burden of disease based on the LMIC metrics, but we also provide alternative calculations with the high-income parameters in Table S12.

Data Gaps

A recent review proposed a comprehensive research agenda relating to IWS *(2)*. Our study further supports this agenda by identifying key data gaps for estimating the health risks attributable to IWS at the population level. First, there is a clear need for direct pathogen measurements from IWS networks in a range of settings, as water quality impacts may vary widely depending on local conditions. Such measurements could be used as direct input for a refined IWS risk assessment and could also be used to develop more robust pathogen to indicator ratios that can be applied to specific settings *vis a vis* fecal indicator measurements. Additionally, for enumeration of fecal indicators, larger volumes of water should be assayed to lower the detection limit to levels more appropriate for risk assessment. Another research area concerns consumer behavior with regard to tap water consumption, household water management and treatment, and household water contamination. Our risk assessment utilized tap water consumption data from settings that are probably not representative of the complex water management behavior often observed among IWS users. A more accurate estimate of the health risks associated with IWS must include these household behaviors in the exposure assessment model. This study also underscores the need for dose-response models that are specific to LMIC settings where acquired immunity, co-infections, and host susceptibility could dramatically alter the infection probabilities associated with ingesting microbial pathogens. Lastly, there is a need for a more robust estimate of the global population served by IWS. The estimate used in this analysis was based on the projection of IBNET data onto the JMP estimates of the global population served by piped-on-premise water supplies, and a simple dichotomy between “intermittent” and “continuous” without accounting for the degree of intermittency *(1)*. It is likely that this underestimates the total number of people served by IWS.

Policy Implications

Piped water supplies rely on multiple barriers including pipeline integrity, positive pressure, and chlorine residual to maintain the safety of the drinking water they deliver *(70)*. These barriers, traditionally considered redundant, are more likely to fail simultaneously in the resource-constrained settings where IWS is prevalent. Our risk assessment indicates that the 925 million users of IWS are likely exposed to

DALY burdens that exceed the WHO health threshold for each of the three reference pathogens considered. The predominance of risk due to the bacterial and viral pathogens in our estimate underscore the importance of an adequate chlorine residual in IWS distribution networks as a potential strategy to mitigate health impacts in the absence of massive investments to upgrade piped networks. Similarly, proper and consistent household water treatment and storage could mitigate the microbial risks of piped water supplies that are operated intermittently *(71)*.

The Millennium Development Goal era has seen rapid expansion in coverage of piped water supplies *(6)*, delivering a wide range of health and non-health benefits to communities. Increasing urbanization and population growth are likely to continue this trend. As more households connect to water supply networks, however, greater attention is needed on microbial risks associated with distribution systems, including those associated with intermittent function. Accounting for these risks highlights the need for continued investment in provision of microbiologically and chemically safe water globally.

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SUPPORTING INFORMATION

Supporting information accompanying this manuscript includes the following: Table S1: Summary of studies measuring fecal indicator bacteria in an IWS; Figure S1: Reported measures of central tendency and range for studies measuring fecal indicators in an IWS; Table S2: Summary of the epidemiological evidence concerning IWS and diarrheal disease; Figure S2: Boxplots of field observed and modeled *E. coli* counts; Figure S3: Frequency distributions of field observed and modeled *E. coli* counts; Figure S4: Cumulative distributions of field observed and modeled *E. coli* counts; Figure S5: Screening flow chart for IBNET utility records; Table S3: Point risk estimates using median *E. coli* counts; Table S4: Point risk estimates using mean *E. coli* counts; Table S5: Point risk estimates using GDWQ data; Figure S6:

Cumulative distributions of daily probability of infection and burden of disease for *Campylobacter*; Figure S7: Cumulative distributions of daily probability of infection and burden of disease for *Cryptosporidium*; Figure S8: Cumulative distributions of daily probability of infection and burden of disease for rotavirus; Table S6: Sensitivity analysis results for *Campylobacter*; Table S7: Sensitivity analysis results for *Cryptosporidium*; Table S8: Sensitivity analysis results for rotavirus; Table S9: Initial IWS population estimate; Table S10: IWS population estimate by WHO region; Figure S9: IWS population map; Table S11: IWS burden of disease tabulations with LMIC rotavirus parameters; Figure S10: Cumulative distributions of annual diarrheal DALYs and deaths by etiology; Table S12: IWS burden of disease tabulations with HIC rotavirus parameters

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