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Safely Managed Hygiene: A Risk-Based Assessment of Handwashing Water Quality

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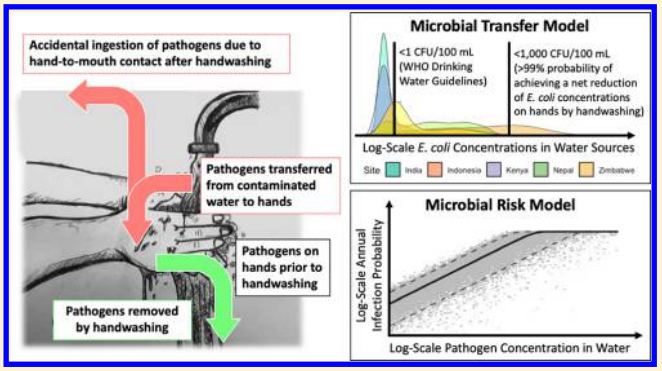
Supporting Information

ABSTRACT: Sustainable Development Goal (SDG) Indicator 6.2.1 requires household handwashing facilities to have soap and water, but there are no guidelines for handwashing water quality. In contrast, drinking water quality guidelines are defined: water must be "free from contamination" to be defined as "safely managed" (SDG Indicator 6.1.1). We modeled the hypothesized mechanism of infection due to contaminated handwashing water to inform risk-based guidelines for microbial quality of handwashing water. We defined two scenarios that should not occur: (1) if handwashing caused fecal contamination, indicated using *Escherichia coli*, on a person's hands to increase rather than decrease and (2) if hand-to-mouth contacts following handwashing caused an infection risk greater than an acceptable threshold. We found water containing <1000 *E. coli* colony-forming units (CFU) per 100 mL removes *E. coli* from hands with>99.9% probability. However, for the annual probability of infection to be <1:1000, handwashing water must contain $<2 \times 10^{-6}$ focus-forming units of rotavirus, $<1 \times 10^{-4}$ CFU of *Vibrio cholerae*, and $<9 \times 10^{-6}$ *Cryptosporidium* oocysts per 100 mL. Our model suggests that handwashing with nonpotable water will generally reduce fecal contamination on hands but may be unable to lower the annual probability of infection risks from hand-to-mouth contacts below 1:1000.



INTRODUCTION

Sustainable Development Goal (SDG) Target 6.2 calls for "adequate and equitable sanitation and hygiene for all" by 2030.[1] The core hygiene indicator requires households to have handwashing facilities with soap and water, where an adequate handwashing facility is defined as "a device to contain, transport, or regulate the flow of water to facilitate handwashing with soap and water".[1] The target is not met when water is not available or when hands are dipped into stored water. The post-2015 WHO/UNICEF Joint Monitoring Program for Water Supply, Sanitation, and Hygiene added a new category for safely managed drinking water, which stipulates that water must be "accessible on premises", "available when needed", and "free from contamination".[1] "Free from contamination" is indicated microbiologically when a 100 mL sample is free of *Escherichia coli* or thermotolerant coliforms. In contrast to drinking water, hygiene has no definition for safe management, and there are currently no guidelines for handwashing water quality. Such a guideline and definition would be especially useful for developing safe handwashing practices in locations where dry sanitation facilities are used or where potable water is scarce. Risk-based drinking water quality guidelines have been established;[2] however, the extent to which handwashing water quality influences disease transmission is unclear.

Handwashing is thought to reduce infectious disease burdens, even in areas where water is likely contaminated.[3,4] However, contaminated handwashing water poses a risk of recontaminating hands with pathogens. For example, a *Shigella dysenteriae* outbreak in Zimbabwe was linked to shared handwashing water.[5] Dipping hands in stored water (which is often more contaminated than source water) was shown to be a risk factor for higher levels of hand contamination after

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handwashing in Zimbabwe.[6] A related study at the same field site further showed that *E. coli* measured on hands after handwashing was significantly associated with *E. coli* concentrations in the handwashing water.[7] In Bangladesh, the use of contaminated pond water instead of cleaner well water was significantly associated with the microbial contamination of hands after rinsing.[8] These studies suggest that more contaminated handwashing water leads to more contaminated hands after handwashing.

The aim of our study was to model the hypothesized mechanism of hand contamination by handwashing water and accidental pathogen doses ingested due to hand-to-mouth contact events, to inform risk-based guidelines for handwashing water quality and safely managed hygiene services. Using Bayesian inference with existing data on virus transfer between water and skin,[9] the efficacy of pathogen removal during handwashing,[10] and fecal indicator concentrations in handwashing water and on hands before and after handwashing,[7] we modeled the overall reduction and addition of health-related microorganisms during handwashing [microbial transfer model (Figure 1)]. We then extended this model to create a quantitative microbial risk assessment (QMRA) model [QMRA model (Figure 1)] by incorporating microbial transfer from hands to saliva[11] and estimating the pathogen dose ingested accidentally due to hand-to-mouth contacts after handwashing and the corresponding probability of infection (individually) for the following reference pathogens: enteropathogenic and enterotoxigenic *E. coli*, *Salmonella enterica* (serovar Typhi), *Shigella flexneri*, *Vibrio cholerae*, *Cryptosporidium* spp., *Giardia* spp., rotavirus, and norovirus. These nine reference pathogens include those that are responsible for most of the moderate-to-severe diarrheal disease burden in developing countries[12] and other pathogens of concern in densely populated areas where waterless sanitation systems are common.

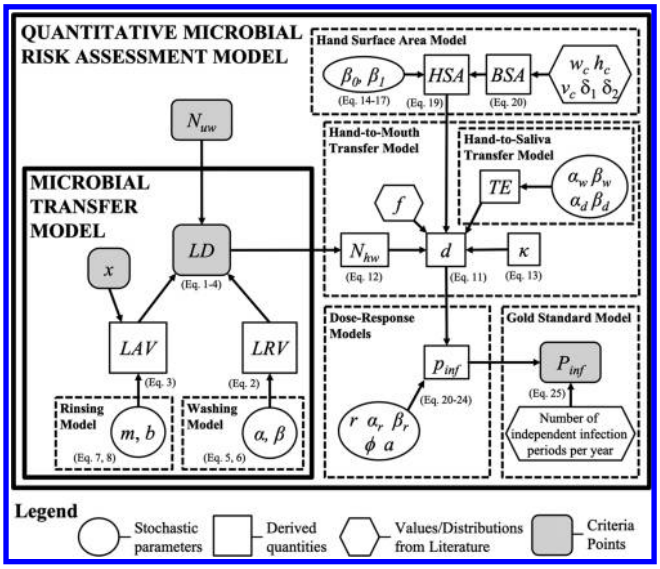

Figure 1. Schematic showing microbial transfer and QMRA models, including models for hand surface area, hand-to-mouth transfer, dose–response, and annualizing probability of infection. Values shown in the model schematic are stochastic parameters (circles and ovals), derived quantities (squares), or data or distributional assumptions obtained from the literature (hexagons). The numbers in the parentheses correspond to the equations described in the text. Criteria for the failure scenarios (gray shaded nodes) include the $\log_{10}$ difference in pathogen concentrations on a person's hands before and after handwashing (LD), which is set to a target value of <0 (i.e., the concentration must decrease after hands are washed) for the microbial transfer model, and the annual probability of infection (P_{inf}), which is set to target values of 1:100, 1:1000, and 1:10000 for the QMRA model. The ability of handwashing practices to meet these criteria was a combined effect of the concentration of pathogens in the handwashing water (x) and the initial concentration of pathogens on a person's hands prior to handwashing (N_{uw}).

METHODS

We linked seven existing models (Figure 1) using Bayesian inference within a QMRA framework to evaluate two scenarios that would cause the failure of handwashing as an effective health intervention. The first, a microbial transfer model, evaluates the scenario in which water used for handwashing adds more microorganisms to a person's hands than are removed by handwashing. In this scenario, the model is a general microbial transfer model with no parameters considered to be specific to any given pathogen or indicator. For the sake of simplicity, we discuss this model using *E. coli* because *E. coli* is a commonly used indicator of fecal contamination. The second, a QMRA model, evaluates the scenario in which hand-to-mouth contacts following handwashing result in a risk of infection greater than a threshold of 1:1000 due to exposure to pathogens from the handwashing water as determined using nine reference pathogens. Thresholds of 1:100 and 1:10000 were also evaluated for comparison (Supporting Information).

Microbial Transfer Model: Evaluating Handwashing Efficacy. To evaluate the first failure scenario (if using impaired handwashing water adds more *E. coli* to a person's hands than are removed by handwashing), we used a microbial transfer model that infers the $\log_{10}$ change in *E. coli* concentrations on hands before and after handwashing, based on removal and re-addition from contaminated rinsing water (Figure 1).[9] The $\log_{10}$ difference in pathogen concentrations on hands before and after handwashing was modeled with LD[x] as the difference between the $\log_{10}$ reduction value (LRV) from handwashing and the $\log_{10}$ addition value (LAV) for new pathogens added to the skin from rinsing water (eq 1). LRV was modeled as a gamma distribution (eq 2), and LAV as a log–linear regression where x is the pathogen concentration in water contacting the skin (eq 3).[9]

$$\mathrm{LD}[x] = \mathrm{LAV}[x] - \mathrm{LRV} \quad (1)$$

$$\mathrm{LRV} \sim \mathrm{gamma}(\alpha, \beta) \quad (2)$$

$$\mathrm{LAV}[x] = m \log_{10}(x) + b \quad (3)$$

Data from a study[7] of *E. coli* concentrations on the hands of 142 adults in Zimbabwe before and after handwashing were used to calculate the $\log_{10}$ differences (y_i) in *E. coli* concentrations that, when paired with corresponding *E. coli* concentrations (x_i) in the water used by each subject for handwashing, were used to infer model parameters. A likelihood function [$P(y_1, y_2, ..., y_{142})|\alpha,\beta,m,b,\sigma$)] (eq 4) and prior distributions (eqs 5–9) were used in a Bayesian framework to generate posterior distributions of α, β, m, b, and the model precision (τ_1) using a Markov Chain Monte Carlo (MCMC) with Gibbs sampling.[13]

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$$y_i \sim \text{normal}\left(\mu_1 = \text{LD}[x_i],\ \sigma_1^2 = \frac{1}{\tau_1}\right) \quad (4)$$

Priors on α and β (eqs 5 and 6) were developed on the basis of a washing model that used data from previous studies of the efficacy of handwashing with non-antimicrobial soap in nonclinical settings.[6,10,14−24] Priors on m and b (eqs 7 and 8) were based on a rinsing model that used data from a previous study of coliphage transfer from water to skin.[9] Posterior distributions for parameters from the washing and rinsing models were used as prior information in the subsequent microbial transfer and QMRA models (see Figure S1).

$$\alpha \sim \text{norm}(\mu = 5.66,\ \sigma = 1.01) \quad (5)$$

$$\beta \sim \text{norm}(\mu = 3.23,\ \sigma = 0.607) \quad (6)$$

$$m \sim \text{norm}(\mu = 0.971,\ \sigma = 0.0217) \quad (7)$$

$$b \sim \text{norm}(\mu = -3.07,\ \sigma = 0.264) \quad (8)$$

$$\sigma_1 \sim \text{gamma}(\alpha_{\sigma_1} = 0.0001,\ \beta_{\sigma_1} = 0.0001) \quad (9)$$

The maximum threshold concentration (X_{max}) for *E. coli* in handwashing water (defined as the concentration at which handwashing neither increases nor decreases the concentration on a person's hands; i.e., LAV[X_{max}] = LRV) was calculated at each iteration of the MCMC as a derived quantity using the posterior distributions from the Bayesian model (eq 10).

$$X_{max} = \frac{\text{LRV} - b}{m} \quad (10)$$

The lower 99th percentile of the posterior distribution for X_{max} is the maximum concentration of *E. coli* in water that, if the water is used for handwashing, reduces the concentration of *E. coli* on a person's hands with a probability of 99%.

Risk Ratios of Avoiding Hand Contamination. If the concentration of *E. coli* (or the concentration of a pathogen) in handwashing water exceeds the maximum recommended values, then a person using that water to wash their hands may actually contaminate their hands more if they wash them (relative to the alternative of not washing them). To put this scenario into further context, we calculated the following risk ratios of avoiding hand contamination: the probability of infection when not washing hands relative to the probability of infection when washing hands using water contaminated with pathogens. Thus, a risk ratio of >1.0 indicates that handwashing reduces risk, and a risk ratio of <1.0 indicates that handwashing increases risk (and thus fails as an effective public health intervention).

QMRA Model: Evaluating Pathogen Transfer from Contaminated Water to Hands. To evaluate the second failure scenario, a QMRA model estimates the probability of infection due to pathogen transfer from contaminated water to hands and from contaminated hands to the mouth (Figure 1). We first assumed that there were no pathogens on hands prior to handwashing and then ran some scenarios assuming a uniform distribution of pathogens on hands, ranging from 10^{-6} to 10^4 per square centimeter, which roughly spans the order of magnitude range of pathogen and fecal indicator concentrations detected on the hands of adults with children under 5 years of age in Tanzania.[25−27]

Hand-to-Mouth Pathogen Transfer. The dose (d) of pathogens accidentally ingested from κ hand-to-mouth contact events was estimated (eq 11)[11] on the basis of the fraction of the hand area that contacts the mouth (f), the hand surface area (HSA),[28] the pathogen transfer efficiency (TE), and the concentration of pathogens on a person's hands (N). This dose can be prior to hand contamination changes following handwashing

$$d = f \times \text{HSA} \times \text{TE} \times N\kappa \quad (11)$$

Equation 11 was used to compute ingested doses as derived quantities at each MCMC iteration. The pathogen concentration on a person's washed hands (N_{hw}; eq 12) was found by rearranging eq 1, where N_{uw} is the pathogen concentration on a person's unwashed hands (prior to handwashing). This allowed for the comparison of two scenarios: one in which a person washes hands (i.e., $N = N_{hw}$) and the other in which the person does not wash hands (i.e., $N = N_{uw}$).

$$N_{hw} = 10^{\log_{10}(N_{uw}) + \text{LD}[x]} \quad (12)$$

There is currently a lack of consensus in the QMRA literature about how to model the dose−response relationship when there are frequent repeated exposures; however, it is generally agreed that the most conservative approach (which may overestimate the risk) is to assume that each exposure represents an independent probability of infection.[29,30] Thus, we assumed that each handwashing event is followed by a hand-to-mouth contact, which contributes to a single independent dose (i.e., $\kappa = 1$). We assumed that people wash hands between 3 and 12 times per day on average,[31] according to a Poisson process with parameter $\lambda \sim \text{unif}(3, 12)$, so that the number of daily doses (N_d) is distributed $N_d \sim \text{Poisson}(\lambda)$. This means that an individual may have multiple opportunities of acquiring an infection each day. To assess the sensitivity of our model to this assumption of independent infection probabilities, we compared our results with those obtained using a different assumption, where all doses ingested over the course of a day accumulate into a single dose (i.e., $\kappa = N_d$) and each day constitutes a single independent infection opportunity.[32]

For HSA in eq 11, we used population-weighted height and weight data from 199 different countries,[33,34] a model relating height and weight to body surface area,[35] and a Bayesian linear regression model relating body surface area to hand surface area (see Estimating Hand Surface Area). For eq 11, we assumed the fraction of the hand contacting the mouth is 11% [standard deviation (sd) of 4.6%]; using moment matching, we specified a beta distribution with parameters $\alpha_f = 5$ and $\beta_f = 40$.[36] We used two uniformly mixed beta distributions (eqs 13−16) to specify the transfer efficiency from fingers to saliva, with means of 20% (sd = 6%) for dry fingers and 58% (sd = 15%) for wet fingers.[9] This mixture distribution assumes an equal probability of a person's hands being wet, dry, or somewhere between those two states. Posterior distributions of the beta distribution parameters for the wet finger and dry finger cases were found using data from ref 9 in a Bayesian model with flat priors [distributed as gamma(0.001, 0.001)] for each of the beta distribution parameters (α_w, β_w, α_d, and β_d).

$$\text{TE} = m_x \text{TE}_w + (1 - m_x)\text{TE}_d \quad (13)$$

$$m_x \sim \text{unif}(0, 1) \quad (14)$$

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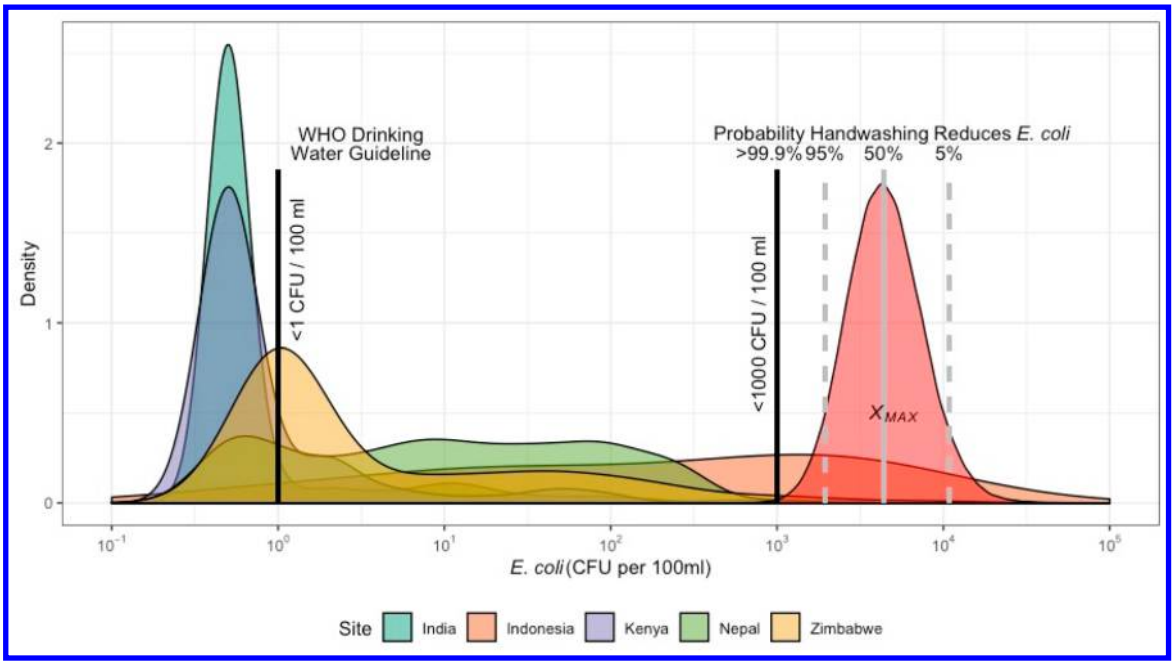

Figure 2. Posterior probability distribution of the maximum threshold for the concentration of *E. coli* in handwashing water, shown as the red distribution. X_{max} is the concentration of *E. coli* in handwashing water for which the number of *E. coli* on hands would be the same after handwashing as it was before handwashing. *E. coli* concentrations in handwashing water corresponding to >99.9, 95, 50, and 5% probabilities that the number of CFUs of *E. coli* will be reduced on hands following handwashing are highlighted using solid black, dashed gray, solid gray, and dashed gray vertical lines, respectively. Distributions derived empirically from data sets on water quality are shown for source waters in the Ciracas Sub District, East Jakarta, Indonesia (orange);[45] source waters in the Kwale District, Kenya (purple);[46] source and stored waters in five districts of the Mid-Western Region, Nepal (green, unpublished), and Hubli-Dharwad, India (blue);[48] and source and stored water used for handwashing in Harare, Zimbabwe (yellow).[7] The WHO Drinking Water Guidelines (2008) of <1 CFU of *E. coli* per 100 mL (which is also the lower limit of detection for the aforementioned studies) is shown as a solid black vertical line.

$$\mathrm{TE}_w \sim \mathrm{beta}(\alpha_w, \beta_w) \tag{15}$$

$$\mathrm{TE}_d \sim \mathrm{beta}(\alpha_d, \beta_d) \tag{16}$$

Estimating Hand Surface Area. Population heights and weights were used to infer a global distribution of hand surface areas.[28,33,34] Hand surface area was modeled with $h[s]$ (eq 17), and regression coefficients (β_1 and β_0) were estimated using Bayesian inference based on the body surface areas (s_j) and corresponding hand surface areas (q_j) for 65 volunteers with a range of different heights and weights,[28] using likelihood function $P(q_1, q_2, ..., q_{65})|\beta_0,\beta_1,\sigma_2)$ (eq 18) and flat prior distributions (eqs 19−21).

$$h[s_j] = \beta_1 s_j + \beta_0 \tag{17}$$

$$q_j \sim \mathrm{normal}\left(\mu_2 = h[s_j],\ \sigma_2{}^2 = \frac{1}{\tau_2}\right) \tag{18}$$

$$\beta_0 \sim \mathrm{unif}(0,\ 1000) \tag{19}$$

$$\beta_1 \sim \mathrm{unif}(0,\ 2) \tag{20}$$

$$\sigma_2 \sim \mathrm{gamma}(\alpha_{\sigma_2} = 0.001,\ \beta_{\sigma_2} = 0.001) \tag{21}$$

The global distribution of hand surface area (HSA) (eq 22) was then calculated using a global distribution of body surface area (BSA), which was modeled deterministically with a weighted geometric equation (eq 23), assuming $\delta_1 = 0.5378$ and $\delta_2 = 0.3964$[37] and using data gathered from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC) Network[38,39] for the mean heights (h_c) and weights (w_c) of adults in 199 different countries. The values for BSA were weighted on the basis of the relative population (ν_c) in each country (eq 23).

$$\mathrm{HSA} = \beta_1 \mathrm{BSA} + \beta_0 \tag{22}$$

$$\mathrm{BSA} = \sum_{c=1}^{N}\left[\left(\frac{\nu_c}{\sum_{c=1}^{N}\nu_c}\right)(0.024265 w_c{}^{\delta_1} h_c{}^{\delta_2})\right] \tag{23}$$

Dose−Response Relationship. For dose−response modeling, we used the exponential function for *Giardia*,[32] the fractional Poisson function for norovirus,[40] and the exact Beta-Poisson function for all other reference pathogens. Dose−response parameter values were inferred using Bayesian inference with challenge study data gathered from QMRAwiki,[32] ref 41, ref 40, and relevant references therein, using an infection end point for all reference pathogens, except for EPEC and ETEC (where diarrhea was the end point). Infection probabilities were computed for each independent infection period at each MCMC iteration using estimated doses and posterior distributions of all parameters.

Dose−response models[32,40] were used to estimate infection probabilities for the reference pathogens. The probability of infection (p_{inf}) was modeled with the exponential model, $f_1[d]$ (eq 24 only), the Beta-Poisson model (eqs 24 and 25), or the fractional Poisson model, $f_2[d]$ (eqs 26 and 27), depending on the pathogen. Dose−response parameters ($\{r, \alpha_r, \beta_r, \phi, a\} \in \theta$) were estimated using a Bayesian framework with data from the literature QMRAwiki,[32−40] likelihood function $P(z_1, z_2, ..., z_n|\theta)$ (eq 28) and flat prior distributions [$r \sim$ unif(0, 1) for the exponential model; $\alpha_r \sim$ gamma(0.01, 0.01) and $\beta_r \sim$

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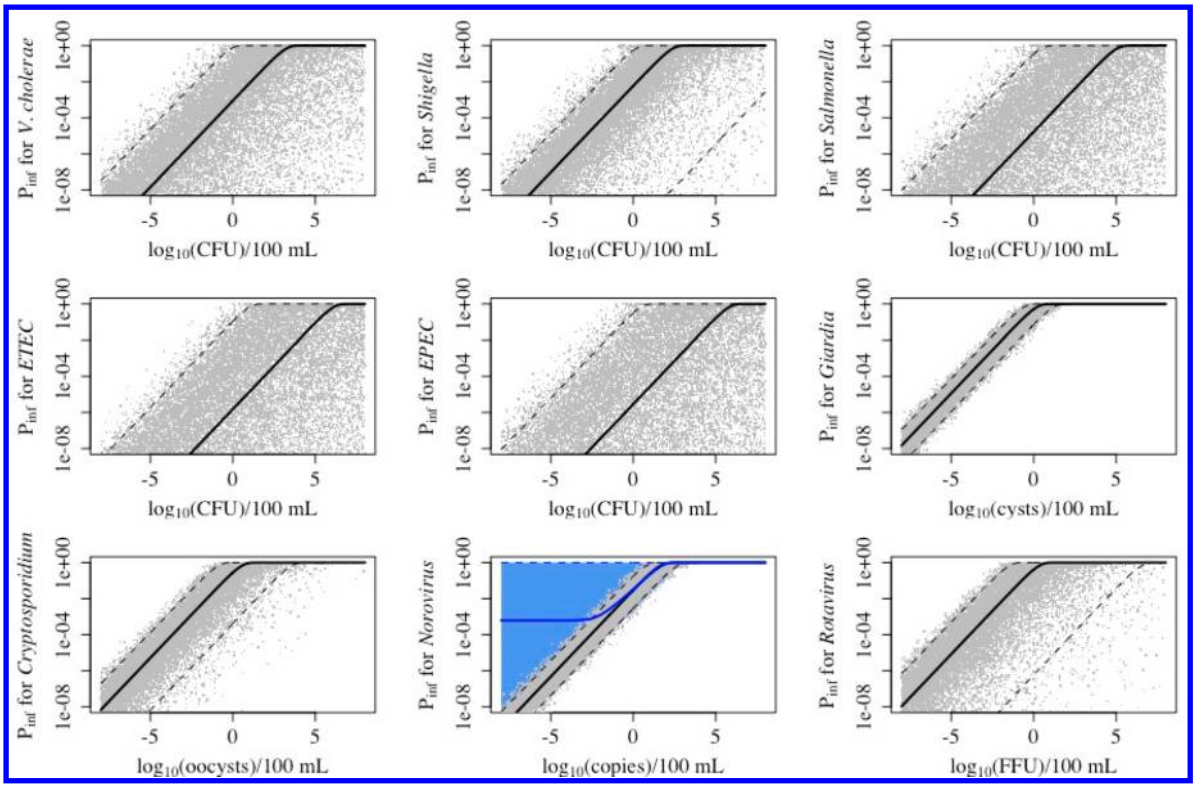

Figure 3. Modeled annual probabilities of infection (P_{inf}) associated with accidental ingestion of pathogens via posthandwashing hand-to-mouth contact events vs the pathogen concentration in handwashing water, under the assumption that hands do not contain any pathogens prior to handwashing. Gray dots show the values from each of the MCMC iterations; median values from the posterior distribution are shown as thick black lines, and the 95% Bayesian credible intervals are shown as thin black dashed lines. The blue lines with blue shading display the median value and associated 95% Bayesian credible interval for the modeled annual probability of infection for norovirus under the assumption that hands have a mean $\log_{10}$-transformed norovirus concentration of −4.85 $\log_{10}$(copies)/cm^2 (sd = 2.91), which is based on a censored regression-on-order statistical analysis of data reported for norovirus GII on the hands of 88 mothers of children under 5 years of age in Tanzania.[25]

gamma(0.01, 0.01) for the Beta-Poisson model, and $\phi \sim$ beta(1, 1) and $a \sim$ beta(1, 1) for the fractional Poisson model].

$$f_1[d] = 1 - e^{-rd} \tag{24}$$

$$r \sim \text{beta}(\alpha_r, \beta_r) \tag{25}$$

$$f_2[d] = \phi(1 - e^{-d/\mu}) \tag{26}$$

$$\mu = \frac{-a}{(1-a)\ln(1-a)} \tag{27}$$

$$z_k \sim \text{binomial}(f_i[d_k], n_k), \text{ where } i = 1 \text{ or } 2 \tag{28}$$

Posterior distributions of dose−response model parameters were used to estimate the probabilities of infection for the doses estimated using eq 11.

Annualizing Infection Probabilities. The adjusted Gold Standard estimator was used to annualize infection probabilities.[42] The Gold Standard estimator is used to estimate annual risk as a product of the probability of all individual infection events and assumes the probabilities of infection events are independent (eq 29). Although the Gold Standard estimate as previously described assumes 365 infection periods per year (daily infection periods), we assumed that as many as $365N_d$ independent exposures are possible per year. We tested the sensitivity of the model to this assumption by modeling an alternative scenario in which a person washing his or her hands multiple times per day would receive a cumulative dose comprising the sum of consecutive doses within that day.

$$P_{inf} = 1 - \prod_{j=1}^{365N_d} (1 - p_{inf,j}) \tag{29}$$

Statistical Methods and Model Sensitivity. Bayesian inference was used to incorporate and propagate uncertainty throughout the model. Posterior distributions of stochastic variables and derived quantities were computed with a Markov Chain Monte Carlo (MCMC) Gibbs sampler (JAGS version 4.2.0)[13] in R version 3.3.2.[43] After adaptation and burn-in of 10000 iterations, we ran three chains of 50000 iterations and checked convergence using the Gelman and Rubin convergence diagnostic potential scale reduction factor (PSRF).[44] Sensitivity was assessed using Spearman correlation coefficients between the model inputs and outputs. The complete R script (with the JAGS script embedded) and data sources (Table S1) are included in the Supporting Information.

RESULTS

Model Convergence. All Bayesian models converged after 50000 iterations as indicated by the fact that the upper 95% confidence limits (CL) of PSRF values for each stochastic node were all below 1.15 with the exception of the α parameter of the *V. cholerae* dose−response model, which had a PSRF value of 1.27 (upper 95% CL = 1.86). The multivariate PSRF value for the overall model was equal to 1.19.

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Microbial Transfer Model: Maximum *E. coli* Concentration in Handwashing Water. The microbial transfer model (Figure 1) predicted that an *E. coli* concentration of 4664 [2108; 11438] CFU per 100 mL in handwashing water corresponds with a 50% [95%; 5%] probability that handwashing reduces *E. coli* concentrations on hands (Figure 2). Handwashing water with less than 1000 CFU per 100 mL would correspond with a >99.9% probability that handwashing reduces *E. coli* concentrations. Overlaid on Figure 2 are distributions derived empirically from data sets of *E. coli* in source water from households in Indonesia (n = 15)[45] and Kenya (n = 139),[46] source and stored water in Nepal (n = 799)[47] and India (n = 1774),[48] and handwashing water from households in Zimbabwe (n = 142).[7]

QMRA Model: Maximum Pathogen Concentrations in Handwashing Water. The QMRA model (Figure 1) estimates the annual probabilities of infection associated with accidental ingestion of pathogens via posthandwashing hand-to-mouth contact events versus the pathogen concentration in handwashing water, assuming no initial hand contamination (Figure 3). The model informs the maximum allowable pathogen concentrations in handwashing water to reduce annual infection probabilities to <1:1000 (Table 1; maximum pathogen concentrations associated with thresholds of <1:100 and <1:10000 are provided in Table S2 for comparison). Conservatively assuming that each infection results in a diarrheal illness with a low fatality rate, the 1:1000 probability is roughly equivalent to an annual burden of 10^{-6} disability adjusted life years (DALYs) per person and a 1 in 10 risk of illness over a lifetime.[2]

Table 1. Maximum Tolerable Pathogen Concentrations (per 100 mL) in Handwashing Water for the Annual Probability of Infection (P_{inf}) Threshold of 1:1000, under the Assumptions That (1) Hands Did Not Contain Any Pathogens Prior to Handwashing and (2) Each Handwashing Event Represents an Independent Dose with an Independent Probability of Infection[a]

reference pathogen	units[b]	pathogen concentration (per 100 mL) corresponding to an annual P_{inf} of ≤1:1000 (with 95% probability)
V. cholerae	CFU	$<1 \times 10^{-4}$
S. flexneri	CFU	$<2 \times 10^{-4}$
S. enterica Typhi	CFU	$<5 \times 10^{-4}$
E. coli (ETEC)	CFU	$<2 \times 10^{-3}$
E. coli (EPEC)	CFU	$<4 \times 10^{-4}$
Giardia	no. of cysts	$<1 \times 10^{-5}$
Cryptosporidium	no. oocysts	$<9 \times 10^{-6}$
norovirus	GC	$<4 \times 10^{-4}$
rotavirus[c]	FFU	$<2 \times 10^{-6}$

[a]The concentrations correspond with a 95% probability that the risk level for the population will be equal to or below the specified threshold of a 1:1000 annual probability of infection. [b]Units include colony-forming units (CFU), gene copies (GC), and focus-forming units (FFU). [c]Rotavirus is primarily a risk for unvaccinated children under 5 years of age, as most older children and adults have acquired immunity due to exposure and/or vaccinations.

Relationship between Pathogen Concentration in Handwashing Water and the Risk Ratios. The risk ratio of not washing hands relative to washing hands asymptotes at 1.0 with increasing concentrations of pathogens on hands. This finding implies that handwashing does not reduce risks when hands are heavily contaminated before handwashing (Table 2).

Table 2. Maximum Numbers of Pathogens That Can Be on a Person's Hands for Handwashing Still To Be an Effective Intervention Using Handwashing Water That Is Free of Pathogens

	maximum concentration on soiled hands[a]		
reference pathogen	units[b]	per cm^2	per hand
V. cholerae	CFU	0.063	27
S. flexneri	CFU	0.072	30
S. enterica Typhi	CFU	0.21	90
E. coli (ETEC)	CFU	0.68	285
E. coli (EPEC)	CFU	0.13	56
Giardia	no. of cysts	0.0089	4
Cryptosporidium	no. of oocysts	0.0056	2
norovirus	GC	0.19	80
rotavirus	FFU	0.0017	1

[a]Based on the weighted average hand surface areas for people from different countries throughout the world (using data from the NCD-RisC Network).[38,39] [b]Units include colony-forming units (CFU), gene copies (GC), and focus-forming units (FFU).

When hands are contaminated with pathogens above a certain threshold (Table 2), the concentration of pathogens on hands even after handwashing remains high enough such that the risk of infection from subsequent hand-to-mouth contacts does not change. For example, when the average concentration of *S. flexneri* on soiled hands is >30 CFU per hand, handwashing (even if the water is free of *S. flexneri*) removes some of the *S. flexneri*, but enough *S. flexneri* remain such that the risk of infection from subsequent hand-to-mouth contacts is not changed. Of note, for rotavirus, *Cryptosporidium*, and *Giardia*, the maximum average concentrations were extremely low (1, 2, and 4, respectively), indicating that if a person contaminates their hands with even a low number of those pathogens, they may be at risk of infection.

Within the linear range of the dose–response relationships, the relationship between the $\log_{10}$ concentration of pathogens in handwashing water and the $\log_{10}$-transformed value of the risk ratio for infection is linear with a slope of ~1.0. For each $\log_{10}$ reduction of pathogens in handwashing water, the risk ratio increases by approximately 1 order of magnitude. Thus, if a person reduces the concentration of pathogens in their handwashing water by 1 order of magnitude, they are ~10 times less likely to obtain an infection from handwashing with that water.

Model Sensitivity. Spearman's correlation coefficients between the model inputs and outputs were generally positive, especially for Beta Poisson dose–response model parameter α for *V. cholerae*, *Shigella*, *Salmonella*, ETEC, EPEC, and rotavirus (correlation matrices provided in Figure S2). Other than the dose–response parameters, the parameter with the next-highest positive correlation with the model outputs was the assumed number of times hands were washed, which had Spearman's correlation coefficients that ranged from 0.031 to 0.051. The estimated $\log_{10}$ reduction value achieved by handwashing had the strongest negative correlation with the estimated infection probabilities. The assumption about the size of the dose and the number of independent infection probability events in a year influenced the posterior distributions of all predicted values but only slightly. For

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example, the order of magnitude change in the predicted X_{max} quantiles was <0.01.

DISCUSSION

Policy Implications. Hand hygiene is a cost-effective intervention for reducing diarrheal disease, yet it is poorly practiced globally.[4] As such, the SDGs incorporate universal access to adequate hygiene within Target 6.2, which is measured via Indicator 6.2.1, the proportion of the population using safely managed sanitation services and basic hygiene services, the latter of which is defined as a handwashing facility with soap and water.[49] The perceived mechanism of the health benefit derived from hand hygiene is the removal of pathogens from hands to reduce subsequent exposures and infection risks. To achieve this, washing hands is promoted at times when pathogen contamination is highest (i.e., after defecating and changing diapers) and before exposure is likely (i.e., before eating and preparing food). **However, our study shows that when water sources are contaminated, the most effective hand hygiene interventions may be more nuanced**. Washing hands with water containing pathogens may add pathogens to hands, so this is only effective at reducing risks if the rate of pathogen removal exceeds the rate of addition.

Generally, Handwashing with Nonpotable Water Will Reduce the Concentration of Pathogens on a Person's Hands. In our microbial transfer model, which is a general microbial transfer model with no parameters specific to any given pathogen or indicator, we show that handwashing with water containing up to 1000 pathogens per 100 mL will reduce the concentration of pathogens on that person's hands with >99.9% likelihood. Handwashing with nonpotable water, even it if contains low concentrations of pathogen, will still provide a net reduction in pathogen contamination on hands. In the vast majority of households in low- and middle-income countries, handwashing with untreated, locally available, water supplies is likely to provide a net reduction in pathogen contamination on hands. A review and meta-analysis of household water sources in low- and middle-income countries showed that even though many water sources in these countries do not meet the drinking water standards, 30 of 31 studies reported median *E. coli* concentrations of <1000 per 100 mL, and 29 of 30 studies reported median thermotolerant coliform concentrations of <1000 per 100 mL. Assuming *E. coli* are a conservative indicator of pathogen contamination in drinking water, households using handwashing water with <1000 *E. coli* per 100 mL are likely to observe a reduction in hand contamination from handwashing.

Households with Severely Impaired Water Supplies May Not Benefit from Handwashing. Handwashing with water containing more than 4664 *E. coli* per 100 mL results in a 50% likelihood that handwashing increases the *E. coli* contamination on hands as the water transfers more *E. coli* to your hands than it removes. Handwashing interventions, although generally effective, occasionally fail to reduce hand contamination and/or diarrheal disease.[50−52] Failure is often attributed to insufficient uptake, but our findings suggest a new potential mechanism: ineffective handwashing due to inadequate water quality. Settings where frequencies of hand contamination and/or diarrheal disease are high may also suffer from poor quality handwashing water. In these settings. handwashing interventions would need to address not only infrastructure (handwashing stations with soap and water) and behavior change but also water quality. As previously discussed, the number of households with water quality insufficient for handwashing is low but not negligible. These households should treat all water supplies in the home, including water used for handwashing.

Although Handwashing with Nonpotable Water May Reduce Hand Contamination, Annual Risks of Infection from Hand-to-Mouth Contacts May Remain above an Acceptable Level of Risk. For the nine reference pathogens modeled in this study, consistent daily exposures to low levels of pathogen contamination in handwashing water may lead to annual infection probabilities that exceed 1:1000 (e.g., Table 1). Handwashing water transfers pathogens to hands; even if the total number of pathogens on hands is reduced following handwashing, the pathogens transferred to hands from nonpotable water pose a risk of infection from subsequent hand-to-mouth contacts. The sensitivity analysis showed that this risk is mildly correlated with the number of times per day a person washes their hands, meaning that a person with a highly contaminated handwashing water source will increase their risks of infection if they wash their hands more frequently. In summary, handwashing with nonpotable water may provide a net benefit (reduces pathogen loads on hands) but nevertheless be a substantial source of infection risk. Of course, for someone without any pathogens on their hands prior to handwashing, washing with a water source with any level of pathogen contamination has the possibility of transferring some pathogens to the hands, which would increase infection risks.

Hand Contamination Is Understudied, yet Our Model Demonstrates That It Is an Important Driver of Hand Hygiene Efficacy. Handwashing will not reduce the annual probability of infection when pathogen contamination on hands (prior to handwashing) exceeds certain thresholds (Table 2). This phenomenon is due to both the limited $\log_{10}$ reduction achieved during handwashing and the fact that daily exposures over the course of a year, even if they are small, can cause nearly 100% probabilities of infection. For many pathogens (i.e., rotavirus, norovirus, and *Cryptosporidium*), this threshold is so low that people in certain family roles or occupations may experience risks that cannot be precluded by handwashing alone. For example, in 9 of 88 Tanzanian households visited, Mattioli et al. detected norovirus GII on the hands of mothers with children under 5 years of age at concentrations as high as 18884 gene copies (GC) per two hands.[25] This concentration is above the maximum threshold identified in Table 2, suggesting that handwashing alone may not reduce risks in areas with high background hand contamination, and additional intervention strategies complementing handwashing may be needed. Examples include waterless hand sanitizers, personal protective equipment during activities that lead to hand contamination, or other interventions to reduce the sources of hand contamination. To determine the most effective interventions, it is necessary to have a better understanding about both the sources and distribution of pathogen concentrations on people's hands. Surprisingly, there are very few studies in the scientific literature that report this type of data.

The Term "Safely Managed" Offers an Opportunity To Make Improvements to Handwashing Facilities Similar to the Improvements Achieved with Drinking Water and Sanitation Services within the SDGs. Our findings suggest that handwashing water quality influences both handwashing effectiveness (as indicated by the $\log_{10}$ reduction value) and

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the subsequent risk of infection from hand-to-mouth contacts. To eliminate handwashing water as a source of new infections, handwashing water would need to be free from fecal contamination, similar to that for drinking water. However, handwashing with nonpotable or untreated water is still likely beneficial. Therefore, treatment or testing of handwashing water may not be practical or, as our study suggests, useful in all communities, especially where limited resources might be better spent on alternative interventions (i.e., improving drinking water supplies and/or sanitation services). Handwashing facilities currently meet the definition of "basic" if both soap and water are available on premises; there is no "safely managed" definition within the current WHO/UNICEF Joint Monitoring Program. Applying the term "safely managed" offers an opportunity to improve handwashing facilities, for example, to account for the microbial quality of the water on premises, either measured directly or inferred from the drinking water quality data. Other characteristics, such as uptake of handwashing facilities, could also be considered under "safely managed". Further recommendations for this approach are outside of the scope of this work, as guidelines are influenced by not only risk assessment but also practicality, feasibility, and costs.

Limitations. Our model has several limitations that suggest the need for further data collection. First, in the absence of data on pathogens added to hands from contaminated water, we used data from a study done with coliphage, assuming it would be representative of all pathogens.[9] Second, our model makes no assumption about hand drying, although the use of a clean cloth to dry hands further reduces pathogen contamination[53] and the use of an unclean cloth may further contaminate hands. The availability and use of clean cloths after handwashing would lead our conclusions to be conservative (e.g., more protective of health). Third, we assumed three times per day as a lower bound for handwashing frequency, which may be an overestimate, although the sensitivity analysis suggests handwashing frequency has a minimal impact on the subsequent probability of infection from handwashing with nonpotable water (Table S2). While a person with pathogens on their hands prior to handwashing would have a greater relative risk of infection if they washed their hands less frequently with sterile water (Figure S3), the additional risk resulting from the use of nonpotable handwashing water (instead of pathogen-free handwashing water) would be lower with less frequent handwashing. Fourth, the model assumes infection risks from hand contamination are driven by hand-to-mouth contacts; other risks such as pathogen transfer from hands to food or water were not considered due to model complexity and uncertainty but are likely non-negligible transmission pathways.

The modeling structure also has limitations. First, the model assumed a uniform distribution of pathogens in handwashing water over time and an even distribution of pathogens across the surface of the hand. To establish the maximum allowable concentration of pathogens in handwashing water on the basis of the set criterion points for the annual probability of infection (i.e., 1:1000), we relied on an assumption of an equal likelihood of pathogen contamination in handwashing water for every handwashing event over a given year (e.g., Figure 3). While this exercise is informative for understanding the average maximum allowable pathogen concentrations in handwashing water, it may not be a realistic representation of how pathogens are distributed in handwashing water. Depending on the nature of the water source, contamination may be highly variable and dependent on the presence or absence of factors that are influential in the fecal contamination of water (e.g., an outbreak event, seasonal livestock grazing, and weather or climatic patterns). For example, many pathogens (e.g., norovirus and rotavirus) have strong seasonal trends. Modeling variation in pathogen contamination (for example, using truncated instead of uniform or log-normal distributions) results in higher tolerable maximum pathogen concentrations on the days when there is an active source of the pathogen if the water source is pathogen-free during other days (results not shown). In summary, the annual probability of infection (and therefore also the maximum pathogen concentration in water) is highly influenced by the number of days in the year when there is contamination of the water source by a particular pathogen. This is not reflected in the sensitivity analysis reported herein. Second, we assumed an even distribution of pathogens across the surface of the hand. Pathogens are more likely heterogeneously distributed over the hands. The parts of the hand most often in contact with the mouth (fingers and finger tips) are also more likely contaminated via surface contact prior to handwashing. Experimental and modeling work is needed to better understand pathogen distribution on the surface of hands and the impact of heterogeneity on handwashing efficacy and risks from hand-to-mouth contacts.[54]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.8b06156.

Data sources used in the model, including electronic retrieval locations; comparison of posterior and prior distributions for the washing model, rinsing model, and microbial transfer model; model sensitivity analysis; maximum tolerable pathogen concentrations in handwashing water for annual probabilities of infection of 1:100 and 1:10000; risk ratios of the probability of infection when not washing hands relative to probability when washing hands with water without pathogens as a function of the number handwashings per day; and complete R and JAGS script used for the model and figure and table generation (PDF)

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Notes

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REFERENCES

(1) World Health Organization (WHO) and the United Nations Children's Fund (UNICEF). WASH in the 2030 agenda: New global indicators for drinking water, sanitation and hygiene. 2017.

(2) Guidelines for Drinking-water Quality [electronic resource]: Incorporating 1st and 2nd addenda, Vol. 1, Recommendations; 9241547618; World Health Organization: Geneva, 2008.

(3) Luby, S. P.; Halder, A. K.; Tronchet, C.; Akhter, S.; Bhuiya, A.; Johnston, R. B. Household characteristics associated with handwashing with soap in rural Bangladesh. *Am. J. Trop. Med. Hyg.* **2009**, *81*, 882−887.

(4) Freeman, M. C.; Stocks, M. E.; Cumming, O.; Jeandron, A.; Higgins, J.; Wolf, J.; Pruss-Ustun, A.; Bonjour, S.; Hunter, P. R.; Fewtrell, L.; Curtis, V. Hygiene and health: Systematic review of handwashing practices worldwide and update of health effects. *Trop. Med. Int. Health* **2014**, *19* (8), 906−916.

(5) Midzi, S. M.; Tshimanga, M.; Siziya, S.; Marufu, T.; Mabiza, E. T. An outbreak of dysentery in a rural district of Zimbabwe: the role of personal hygiene at public gatherings. *Cent. Afr. J. Med.* **2000**, *46* (6), 150−3.

(6) Friedrich, M. N. D.; Julian, T. R.; Kappler, A.; Nhiwatiwa, T.; Mosler, H.-J. Handwashing, but how? Microbial effectiveness of existing handwashing practices in high-density suburbs of Harare, Zimbabwe. *Am. J. Infect. Control* **2017**, *45* (3), 228−233.

(7) Navab-Daneshmand, T.; Friedrich, M. N. D.; Gächter, M.; Montealegre, M. C.; Mlambo, L. S.; Nhiwatiwa, T.; Mosler, H.-J.; Julian, T. R. Escherichia coli contamination across multiple environmental compartments (soil, hands, drinking water, and handwashing water) in urban Harare: Correlations and risk factors. *Am. J. Trop. Med. Hyg.* **2018**, *98* (3), 803−813.

(8) Hoque, B. A.; Mahalanabis, D.; Alam, M. J.; Islam, M. S. Post-defecation handwashing in Bangladesh: Practice and efficiency perspectives. *Public Health* **1995**, *109*, 15−24.

(9) Pitol, A. K.; Bischel, H. N.; Kohn, T.; Julian, T. R. Virus transfer at the skin-liquid interface. *Environ. Sci. Technol.* **2017**, *51* (24), 14417−14425.

(10) Foddai, A. C.; Grant, I. R.; Dean, M. Efficacy of instant hand sanitizers against foodborne pathogens compared with hand washing with soap and water in food preparation settings: A systematic review. *J. Food Prot.* **2016**, *79* (6), 1040−1054.

(11) Julian, T. R.; Canales, R. A.; Leckie, J. O.; Boehm, A. B. A model of exposure to rotavirus from nondietary ingestion iterated by simulated intermittent contacts. *Risk Anal.* **2009**, *29* (5), 617−32.

(12) Kotloff, K. L.; Nataro, J. P.; Blackwelder, W. C.; Nasrin, D.; Farag, T. H.; Panchalingam, S.; Wu, Y.; Sow, S. O.; Sur, D.; Breiman, R. F.; et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet* **2013**, *382* (9888), 209−22.

(13) Plummer, M. JAGS: A program for analysis of Bayesian graphical models using Gibbs sampling. *Proceedings of the 3rd International Workshop on Distributed Statistical Computing*; 2003.

(14) Manthriratna, G. A. Efficacy of handwashing as an aid in the control of rotavirus and Giardia transmission. University of Arizona, Tucson, AZ, 1989.

(15) Schurmann, W.; Eggers, H. J. An experimental study on the epidemiology of enteroviruses: water and soap washing of poliovirus 1–contaminated hands, its effectiveness and kinetics. *Med. Microbiol. Immunol.* **1985**, *174* (5), 221−36.

(16) Sickbert-Bennett, E. E.; Weber, D. J.; Gergen-Teague, M. F.; Sobsey, M. D.; Samsa, G. P.; Rutala, W. A. Comparative efficacy of hand hygiene agents in the reduction of bacteria and viruses. *Am. J. Infect. Control* **2005**, *33* (2), 67−77.

(17) Sickbert-Bennett, E. E.; Weber, D. J.; Gergen-Teague, M. F.; Rutala, W. A. The effects of test variables on the efficacy of hand hygiene agents. *Am. J. Infect. Control* **2004**, *32* (2), 69−83.

(18) Mittermayer, H.; Rotter, M. Vergleich der Wirkung von Wasser, einigen Detergentien und xthylalkohol auf die transiente Flora der Hande. *Zentralbl. Bakteriol., Mikrobiol. Hyg., Abt. 1, Orig. B* **1975**, *160* (2), 163−72.

(19) Liu, P.; Yuen, Y.; Hsiao, H. M.; Jaykus, L. A.; Moe, C. Effectiveness of liquid soap and hand sanitizer against Norwalk virus on contaminated hands. *Appl. Environ. Microbiol.* **2010**, *76* (2), 394−9.

(20) Lages, S. L.; Ramakrishnan, M. A.; Goyal, S. M. In-vivo efficacy of hand sanitisers against feline calicivirus: a surrogate for norovirus. *J. Hosp. Infect.* **2008**, *68* (2), 159−63.

(21) Kampf, G.; Kramer, A. Epidemiologic background of hand hygiene and evaluation of the most important agents for scrubs and rubs. *Clin. Microbiol. Rev.* **2004**, *17* (4), 863−93.

(22) Gehrke, C.; Steinmann, J.; Goroncy-Bermes, P. Inactivation of feline calicivirus, a surrogate of norovirus (formerly Norwalk-like viruses), by different types of alcohol in vitro and in vivo. *J. Hosp. Infect.* **2004**, *56* (1), 49−55.

(23) Edmonds, S. L.; McCormack, R. R.; Zhou, S. S.; Macinga, D. R.; Fricker, C. M. Hand hygiene regimens for the reduction of risk in food service environments. *J. Food Prot.* **2012**, *75* (7), 1303−9.

(24) Ansari, S. A.; Sattar, S. A.; Springthorpe, V. S.; Wells, G. A.; Tostowaryk, W. In vivo protocol for testing efficacy of hand-washing agents against viruses and bacteria: experiments with rotavirus and Escherichia coli. *Appl. Environ. Microbiol.* **1989**, *55* (12), 3113−8.

(25) Mattioli, M. C. M.; Davis, J.; Mrisho, M.; Boehm, A. B. Quantification of human norovirus gII on hands of mothers with children under the age of five years in Bagamoyo, Tanzania. *Am. J. Trop. Med. Hyg.* **2015**, *93* (3), 478−484.

(26) Mattioli, M. C.; Boehm, A. B.; Davis, J.; Harris, A. R.; Mrisho, M.; Pickering, A. J. Enteric pathogens in stored drinking water and on caregiver's hands in Tanzanian households with and without reported cases of child diarrhea. *PLoS One* **2014**, *9* (1), e84939.

(27) Pickering, A. J.; Davis, J.; Walters, S. P.; Horak, H. M.; Keymer, D. P.; Mushi, D.; Strickfaden, R.; Chynoweth, J. S.; Liu, J.; Blum, A.; et al. Hands, water, and health: Fecal contamination in Tanzanian communities with improved, non-networked water supplies. *Environ. Sci. Technol.* **2010**, *44*, 3267−3272.

(28) Lee, J.-Y.; Choi, J.-W.; Kim, H. Determination of hand surface area by sex and body shape using alginate. *J. Physiol. Anthropol.* **2007**, *26* (4), 475−483.

(29) Haas, C. N. Microbial dose response modeling: past, present, and future. *Environ. Sci. Technol.* **2015**, *49* (3), 1245−1259.

(30) Pujol, J. M.; Eisenberg, J. E.; Haas, C. N.; Koopman, J. S. The effect of ongoing exposure dynamics in dose response relationships. *PLoS Comput. Biol.* **2009**, *5* (6), e1000399.

(31) Davis, J.; Pickering, A. J.; Rogers, K.; Mamuya, S.; Boehm, A. B. The effects of informational interventions on household water management, hygiene behaviors stored drinking water quality and hand contamination in peri-urban Tanzania. *Am. J. Trop. Med. Hyg.* **2011**, *84*, 184−191.

(32) Center for Advancing Microbial Risk Assessment (CAMRA). Dose Response. Quantitative Microbial Risk Assessment (QMRA) Wiki http://qmrawiki.canr.msu.edu/index.php/Dose_Response (accessed June 25, 2018).

(33) Abarca-Gómez, L.; Abdeen, Z. A.; Hamid, Z. A.; Abu-Rmeileh, N. M.; Acosta-Cazares, B.; Acuin, C.; Adams, R. J.; Aekplakorn, W.; Afsana, K.; Aguilar-Salinas, C. A.; et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: A pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet* **2017**, *390*, 2627−2642.

(34) Bentham, J.; Di Cesare, M.; Stevens, G. A.; Zhou, B.; Bixby, H.; Cowan, M.; Fortunato, L.; Bennett, J. E.; Danaei, G.; Hajifathalian, K.; et al. A century of trends in adult human height. *eLife* **2016**, *5*, e13410.

DOI: 10.1021/acs.est.8b06156
Environ. Sci. Technol. 2019, 53, 2852−2861

(35) Gehan, E. A. a. G.; Stephen, L. Estimation of human body surface area from height and weight. *Cancer Chemother. Rep.* **1970**, *54* (4), 225−235.
(36) AuYeung, W.; Canales, R. A.; Leckie, J. O. The fraction of total hand surface area involved in young children's outdoor hand-to-object contacts. *Environ. Res.* **2008**, *108* (3), 294−299.
(37) Haycock, G. B.; Schwartz, G. J.; Wisotsky, D. H. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J. Pediatr.* **1978**, *93* (1), 62−66.
(38) NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* **2017**, *390* (10113), 2627−2642.
(39) NCD Risk Factor Collaboration (NCD-RisC). A century of trends in adult human height. *eLife* **2016**, *5*, e13410.
(40) Messner, M. J.; Berger, P.; Nappier, S. P. Fractional poisson—a simple dose-response model for human norovirus. *Risk Anal.* **2014**, *34* (10), 1820−1829.
(41) Messner, M. J.; Berger, P. Cryptosporidium infection risk: results of new dose-response modeling. *Risk Anal.* **2016**, *36* (10), 1969−1982.
(42) Karavarsamis, N.; Hamilton, A. Estimators of annual probability of infection for quantitative microbial risk assessment. *J. Water Health* **2010**, *8* (2), 365−373.
(43) R Development Core Team. *R: A language and environment for statistical computing*. http://www.R-project.org/ (accessed July 27, 2018).
(44) Gelman, A.; Rubin, D. B. Inference from iterative simulation using multiple sequences. *Statistics* **1992**, *7*, 457−511.
(45) Putri, L. S. E.; Kustanti, N.; Yunita, E. Effect of land use on ground water quality (a case study from Ciracas Sub District, East Jakarta, Indonesia). *Int. J. Biosci., Biochem. Bioinf.* **2013**, *3* (1), 33.
(46) Mzuga, J. M.; Tole, M. P.; Ucakuwun, E. K. Contamination of groundwater resources by pit latrines in Kwale District, Kenya. *Discovery Innovation* **2001**, *13* (3), 203−212.
(47) Assessing drinking water quality from point of collection to point of use in rural Nepal. UNESCO-IHE Institute for Water Education, 2015.
(48) Kumpel, E.; Nelson, K. L. Comparing microbial water quality in an intermittent and continuous piped water supply. *Water Res.* **2013**, *47* (14), 5176−5188.
(49) United Nations Economic and Social Council. Report of the inter-agency and expert group on Sustainable Development Goal indicators. Statistical Commission, Forty-Seventh Session; 2016; pp 1−62.
(50) Null, C.; Stewart, C. P.; Pickering, A. J.; Dentz, H. N.; Arnold, B. F.; Arnold, C. D.; Benjamin-Chung, J.; Clasen, T.; Dewey, K. G.; Fernald, L. C.; et al. Effects of water quality, sanitation, handwashing, and nutritional interventions on diarrhoea and child growth in rural Kenya: a cluster-randomised controlled trial. *Lancet Global Health* **2018**, *6* (3), e316−e329.
(51) Ercumen, A.; Pickering, A.; Kwong, L. H.; Mertens, A.; Arnold, B. F.; Benjamin-Chung, J.; Hubbard, A. E.; Alam, M.; Sen, D.; Islam, S.; et al. Do sanitation improvements reduce fecal contamination of water, hands, food, soil and flies? Evidence from a cluster-randomized controlled trial in rural Bangladesh. *Environ. Sci. Technol.* **2018**, *52* (21), 12089−12097.
(52) Friedrich, M. N.; Kappler, A.; Mosler, H.-J. Enhancing handwashing frequency and technique of primary caregivers in Harare, Zimbabwe: a cluster-randomized controlled trial using behavioral and microbial outcomes. *Soc. Sci. Med.* **2018**, *196*, 66−76.
(53) Patrick, D.; Findon, G.; Miller, T. Residual moisture determines the level of touch-contact-associated bacterial transfer following hand washing. *Epidemiol. Infect.* **1997**, *119* (3), 319−325.
(54) Christopher, Y.; Semple, S.; Hughson, G.; Cherrie, J. Inadvertent ingestion exposure in the workplace. Health and Safety Executive, 2007.

DOI: 10.1021/acs.est.8b06156
Environ. Sci. Technol. 2019, 53, 2852−2861