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Understanding the Effectiveness of Water, Sanitation, and Hygiene Interventions: A Counterfactual Simulation Approach to Generalizing the Outcomes of Intervention Trials

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Background: While water, sanitation, and hygiene (WASH) interventions can reduce diarrheal disease, many large-scale trials have not found the expected health gains for young children in low-resource settings. Evidence-based guidance is needed to improve interventions and remove barriers to diarrheal disease reduction.

Objectives: We aimed to estimate how sensitive WASH intervention effectiveness was to underlying contextual and intervention factors in the WASH Benefits (WASH-B) Bangladesh cluster-randomized controlled trial.

Methods: The investigators measured diarrheal prevalence in children enrolled in the WASH-B trial at three time points approximately 1 year apart ($n = 17{,}187$ observations). We developed a susceptible–infectious–susceptible model with transmission across multiple environmental pathways and evaluated each of four interventions [water (W), sanitation (S), hygiene (H), and nutrition (N) applied individually and in combination], compliance with interventions, and the impact of individuals not enrolled in the study. Leveraging a set of mechanistic parameter combinations fit to the WASH-B Bangladesh trial using a hybrid Bayesian sampling-importance resampling and maximum-likelihood estimation approach, we simulated trial outcomes under counterfactual scenarios to estimate how changes in six WASH factors (preexisting WASH conditions, disease transmission potential, intervention compliance, intervenable fraction of transmission, intervention efficacy, and community coverage) impacted intervention effectiveness.

Results: Increasing community coverage had the greatest impact on intervention effectiveness (e.g., median increases in effectiveness of 34.0 and 45.5 percentage points in the WSH and WSHN intervention arms when increasing coverage to 20%). The effect of community coverage on effectiveness depended on how much transmission was along pathways not modified by the interventions. Intervention effectiveness was reduced by lower levels of preexisting WASH conditions or increased baseline disease burden. Individual interventions had complementary but not synergistic effects when combined.

Discussion: To realize the expected health gains, future WASH interventions must address community coverage and transmission along pathways not traditionally covered by WASH. The effectiveness of individual-level WASH improvements is reduced more the further the community is from achieving the coverage needed for herd protection. https://doi.org/10.1289/EHP15200

Introduction

Enteric diseases, primarily spread through contact with fecal contamination in the environment (e.g., water, surfaces, and food), are one of the leading causes of morbidity and mortality in young children.[1] Nearly 500,000 children under 5 years of age die from diarrheal disease globally each year,[2,3] and it is hypothesized that repeated subclinical infections may lead to stunted growth.[4] Much of this burden is in low- and middle-income countries (LMICs).[5] Enteric pathogens are transmitted by myriad pathways, including fluids, fomites, food, flies, and fauna, as summarized in the classic "F-diagram."[6] Studying and preventing diarrheal disease is complicated because a diverse array of pathogens can cause similar symptoms,[7,8] pathogens can exploit multiple transmission pathways, and asymptomatic infections can contribute to the community pathogen burden.[9]

Diarrheal disease is greatly reduced in communities with robust water, sanitation, and hygiene (WASH) infrastructure, with mutually reinforcing levels of community and individual protection.[10]

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Household-level WASH improvements can result in considerable reductions in diarrheal disease burden in LMICs, and many WASH interventions—such as improved latrines and handwashing with soap—have demonstrable efficacy to reduce fecal exposure.[11] A recent meta-analysis by Wolf et al. of WASH intervention randomized controlled trials (RCTs) highlighted that WASH interventions reduce diarrhea in children in low-resource settings.[11] However, there is substantial heterogeneity in the effect estimates across the studies, and many large-scale trials reported less-than-expected or null results.[12–18] In particular, the results of the WASH Benefits (WASH-B) Bangladesh and Kenya trials and the Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial, all of which found no impact of WASH on linear growth but some mixed effects on diarrhea, were particular subjects of substantial discussion in the literature.[19–23] The suboptimal performance of the interventions in these trials is likely due to a combination of multiple factors, including incomplete blocking of all transmission pathways (low intervenable fraction, also called completeness), inadequate community coverage of the intervention, or a lack of intervention compliance or efficacy.[20,24] Additionally, a community's preexisting WASH conditions and baseline disease burden can also impact the real-world intervention effectiveness.[20,24] Assessing which factors are the largest barriers to diarrheal disease reduction will aid policymakers, practitioners, and researchers in deciding how best to invest in WASH programs and design the next generation of programs and trials.[19–25]

RCTs are considered the gold-standard for estimating causal relationships, and they are rigorous assessments of a particular intervention within a particular context at a particular point in time. But, their findings do not necessarily generalize to other contexts or conditions—e.g., different populations, disease burdens, pathogens, transmission pathways, and intervention fidelity and adherence—when there are effect modifiers that vary across field settings and intervention implementations.[21,24] Mechanistic infectious disease transmission models, unlike meta-analyses, have the potential to generalize findings by directly accounting for these location-specific contexts and conditions, exploring counterfactual questions through simulation of alternate scenarios, and developing location-specific programmatic targets. This approach is used extensively in other contexts to assess public health interventions or counterfactual conditions.[26–28] A mechanistic, counterfactual approach could lead to better-targeted public health WASH interventions, policy recommendations, and field trials.[29,30]

The aims of this work are to evaluate hypotheses about what led to the suboptimal reductions in diarrhea among intervention households in an RCT (WASH-B Bangladesh) using a compartmental transmission model and to provide a framework to support improved planning of WASH interventions and context-specific WASH programming. We previously developed a model framework accounting for multiple environmental transmission pathways, shared environments, preexisting WASH conditions, and adherence to multiple interventions and applied it to the empirical trial data.[31] In this analysis, we leverage that framework to generate thousands of combinations of coverage, intervention efficacy, and transmission pathway strengths that could reasonably underlie the trial results and then simulate how intervention effectiveness would have been different under alternate scenarios.

Methods

Summary of Approach

In prior work, we developed a general compartmental transmission model framework to explain the outcomes of an RCT.[31] This model framework accounted for how the effectiveness of an intervention, i.e., the observed reduction in diarrhea prevalence in an intervention arm compared to the control arm, depends on six WASH factors:

- Preexisting WASH conditions: Our model accounts for the fact that a fraction of the population may have already had WASH infrastructure comparable to that provided by an intervention trial.
- Disease transmission potential: Our model accounts for the baseline disease prevalence through the basic reproduction number R_0, a summary measure of the disease transmission potential. Note that, given the values of the other WASH factors, there is a one-to-one correspondence between the disease prevalence and the basic reproduction number. In this counterfactual analysis, we parameterized the model using the baseline disease prevalence rather than R_0, as it is what intervention trials measure.
- Intervention compliance: Our model accounts for both intervention fidelity (whether the intervention was delivered) and adherence (whether participants used the intervention), defining compliance as the fraction of participants assigned to and using an intervention.
- Intervenable fraction of transmission: Any individual intervention targets at least one, but often not all, of the transmission pathways that pathogens exploit. Our model accounts for how much transmission was along pathways that the intervention attenuated (even if imperfectly) and how much even a perfect intervention would not have affected. The intervenable fraction will differ for different pathogens and thus will depend on the distribution of pathogens in the local context of a given trial.
- Intervention efficacy: Our model accounts for the fact that interventions do not result in perfect reduction of transmission or shedding.
- Community coverage fraction: Intervention trials typically only provide the intervention to a subset of the population. Our model accounts for the fact that only a fraction of the population may be enrolled in a trial.

In this analysis, we use a multi-intervention version of the model to investigate outcomes in the WASH-B Bangladesh RCT specifically. In prior work, we demonstrated how to find mechanistic parameter sets that were consistent with individual-level diarrheal outcomes.[31] Here, we used these mechanistic parameter sets to simulate what intervention effectiveness would have been in each of the WASH-B Bangladesh trial arms under each of six counterfactuals corresponding to the six WASH factors above, accounting for uncertainty in the parameters underlying the real data (original scenario). By simulating what the intervention effectiveness would have been in the trial under alternate circumstances, we evaluated the extent to which each factor may have contributed to the observed outcomes.

Data

The WASH-B Bangladesh trial was a cluster-randomized trial of the effectiveness of water, sanitation, hygiene, and nutrition interventions, alone and in combination, on diarrhea prevalence and linear growth.[15] The study followed one or more target children born after enrollment, as well as any other children in the compound who were under age 3 at Enrollment. The investigators measured (child–guardian-reported, past-seven-day, all-cause) diarrheal prevalence in these children at three time points approximately 1 year apart (enrollment, year 1, and year 2), comparing mean diarrheal prevalence in years 1 and 2 in each arm to the control arm. Households in the study area were typically organized into compounds in which a patrilineal family shared a common space and resources, such as a water source and latrine. A total of 5,551 compounds were enrolled, contingent on having a pregnant woman in her second trimester residing in the compound during

the enrollment period. These compounds were grouped into 720 clusters. Each cluster was assigned to one of seven arms testing combinations of four interventions: water chlorination (W), a double-pit, pour-flush improved latrine (S), handwashing with soap and water (H), and supplementary nutrition sachets (N). The control arm (C) consisted of 180 compounds, while 90 were assigned to each of the water (W); sanitation (S); handwashing (H); nutrition (N); combined water, sanitation, and handwashing (WSH); and all interventions (WSHN) arms. Intervention compliance, as defined by the investigators, was high—80% or higher in years 1 and 2 in all arms that received the corresponding intervention.[15,32] Specific details on trial design, interventions, and results are published elsewhere.[15,33] We assessed whether any individual was using an intervention or a substantively equivalent preexisting WASH condition through four indicators defined and assessed by the investigators at each time point: detection of free chlorine in drinking water (W), observation of a latrine with a functional water seal (S), observation of a handwashing station with soap and water (H), and caregiver report of child consumption of at least 50% of nutrition sachets consumed (N). The W and H interventions were intended for the households of the target children, but we were not able to determine the household of each child within the compound. For this analysis, we assumed that nontarget children were covered by the interventions; we expect any misspecification to attenuate the estimated efficacy of the W and H interventions.[15] We removed individuals with negative reported ages ($n = 2$), missing reported diarrhea ($n = 2{,}745$), or missing any of the four use indicators ($n = 2{,}660$), which left 17,187 individual observations (76% of the original sample) over the three surveys. The WASH Benefits Bangladesh data is publicly available at https://osf.io/tprw2/.

Ethics

This secondary analysis of publicly available data was determined to be not regulated as human subjects research by the University of Michigan institutional review board (HUM00260701).

Model

Our compartmental transmission model, denoted SISE-RCT, is a susceptible–infectious–susceptible (SIS) model with transmission through environmental (E) compartments and simulated to steady state to approximate an RCT.[31] The SISE-RCT model accounts for the six key mechanistic factors underlying the WASH RCT outcomes described above.

As discussed in the Data section above, the WASH-B Bangladesh trial included 720 clusters of households, each assigned to one of seven arms (control, W, S, H, N, WSH, WSHN). We extended the single-intervention SISE-RCT model to a multi-intervention model by accounting for transmission across three environmental pathways (water, fomites and hands, and all others combined), four interventions applied individually (W, S, H, N) and in combination (WSH, WSHN), and individual-level compliance with interventions or preexisting conditions. In brief, we modeled each of the 720 clusters with susceptible and infectious compartments for each of $2^4 = 16$ combinations of interventions/conditions depending on household compliance; i.e., in every cluster, we modeled the infection prevalence for each combination of having or not having each intervention or equivalent preexisting WASH condition. For example, for a cluster in the WSH arm, we estimated how many people were not using any interventions, how many were using W only, how many were using S only, and etc., and what the infection prevalence was among each group given their collective interaction through the shared environments.

Specifically, for a given cluster, we denoted the fraction of the population that was susceptible to infection and was using intervention(s) or preexisting WASH condition(s) i in $\{0, W, S, H, N, WS, \ldots, WSHN\}$ as S_i, where 0 indicates the use of no intervention or preexisting WASH condition. Analogously, we denoted the fraction of the population that was infected analogously by I_i. Each cluster was simulated separately. The populations with regular and attenuated exposure were modeled in every cluster simulation, accounting for the fraction of the population *a*) enrolled in the study [the community coverage (ω)], *b*) with preexisting WASH conditions (ρ_0), and *c*) complying with the intervention (ρ). Note that ρ_0 and ρ were vectors of length 16 that each sum to 1; i.e., everyone was categorized into one of the 16 exposure groups. For each cluster, the overall fraction of the population in each exposure group (n) was given by the vector:

$$n = (1-\omega)\rho_0 + \omega\rho. \quad (1)$$

That is, the fraction of the population enrolled in the study (ω) followed the intervention compliance distribution of exposure groups (ρ), and the fraction of the population not enrolled ($1-\omega$) followed the preexisting WASH condition distribution of exposure groups (ρ_0). In the control arm, $\rho = \rho_0$.

In this model, the environment was partitioned into the three environmental pathways: water (E_w), fomites and hands (E_f), and all other pathways (E_o). We assumed that chlorination reduced transmission along the water pathway, sanitation reduced shedding into the water pathway, handwashing reduced transmission along the fomite pathway, and nutrition reduced susceptibility (transmission) for all three pathways. For each of the three pathways j, an environmental compartment E_j was characterized by shedding into the environment (α_j), the decay of pathogens in the environment (ξ_j), and the transmission of pathogens from the environment to susceptible individuals (β_j). The relative magnitude of shedding into E_j and relative transmission from E_j for the attenuated compared to the exposed populations were given by ϕ_{α_j} and ϕ_{β_j}, respectively. We also accounted for the possibility that the preexisting conditions were less efficacious than the RCT intervention. Once infected, individuals cleared the infection at rate γ.

The SISE-RCT parameters are given in Table 1, and the model diagram of the multi-intervention SISE-RCT is given in Figure 1, although only two of the sixteen different exposure populations are shown. The full equations are given below (Equation 2). A transmission term $\beta_j E_j$ denotes transmission from the environmental pathway j. The transmission term $\beta_j E_j$ was attenuated by ϕ_{β_j} only for people in an attenuated exposure group (S_i) using an intervention or preexisting condition that reduced transmission from pathway j, and contamination of that environmental pathway was attenuated by ϕ_{α_j} only for infectious people in an exposure group (I_i) using an intervention or preexisting condition that reduced shedding into pathway j. In the following equations, the subscripts w, f, and o represent the water, fomites and hands, and other pathways, respectively. The subscripts 0, W, S, H, N, and any combinations represent the exposure groups as defined above. Parameters, ρ and ρ_0 do not show up in these equations but were accounted for in the constraints, as discussed below. For brevity, we omit the $\frac{dS_i}{dt}$ equations, each of which is given by $\frac{dS_i}{dt} = -\frac{dI_i}{dt}$ for the corresponding subpopulation.

$$\frac{dI_0}{dt} = (\beta_w E_w + \beta_f E_f + \beta_o E_o) S_0 - \gamma I_0,$$

$$\frac{dI_W}{dt} = (\varphi_{\beta_w, W} \times \beta_w E_w + \beta_f E_f + \beta_o E_o) S_W - \gamma I_W,$$

$$\frac{dI_S}{dt} = (\beta_w E_w + \beta_f E_f + \beta_o E_o) S_S - \gamma I_S,$$

Table 1. Parameters of the SISE-RCT model.

Parameter	Definition	Median value
ρ_0	Baseline WASH conditions (fraction of individuals in the community with intervention-level WASH infrastructure)	—
ρ	Compliance (fraction of individuals in intervention arm using intervention)	—
R_0	Transmission potential (basic reproduction number)	1.10
π_c^*	Baseline disease prevalence[a]	6.9%
$R_{0,w}/R_0$	Fraction of transmission along the water pathway	0.23
$R_{0,f}/R_0$	Fraction of transmission along the fomite and hands pathway	0.25
$R_{0,f}/R_0$	Fraction of transmission on pathways not intervened on (i.e., 1 minus the intervenable fraction)	0.52
$1-\varphi_\alpha$	Intervention efficacy for reducing shedding (S, sanitation intervention)	0.23 (S)
$1-\varphi_\beta$	Intervention efficacy for reducing transmission (W, water; H, hygiene; N, nutrition interventions)	0.44 (W), 0.33 (H), 0.16 (N)
ω	Community coverage fraction (fraction of community included in the intervention trial)	5.4%

Note: The SISE-RCT model is a compartmental susceptible–infectious–susceptible (SIS) model with transmission through environmental (E) compartments and simulated to steady state to approximate a randomized controlled trial (RCT). The median value column denotes the median values for the multi-intervention model. Parameters ρ_0 and ρ do not have median values because they are determined by the data. —, no data; WASH, water, sanitation, and hygiene.
[a]Baseline disease prevalence is technically a model output, but we treat it as a parameter because it has a 1-to-1 correspondence with R_0 given the other parameters.

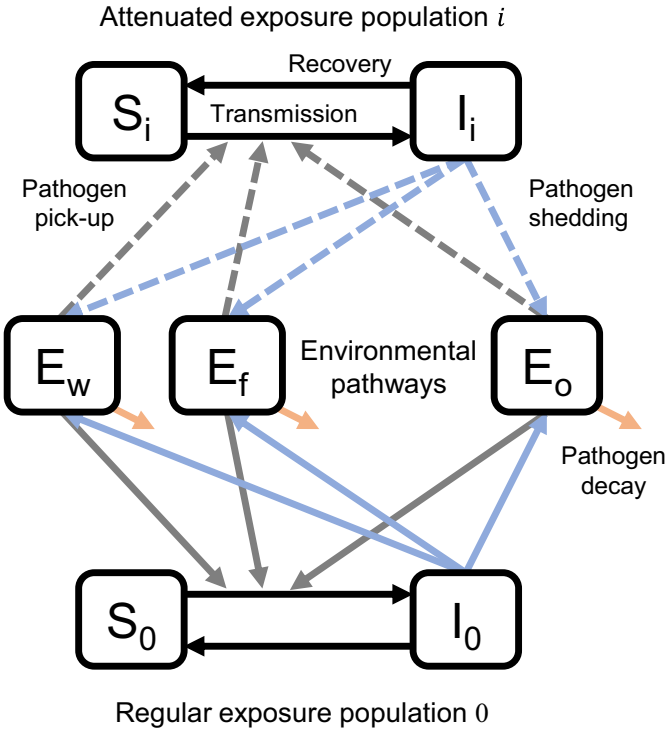

Figure 1. SISE-RCT model diagram with one attenuated exposure population and a regular exposure population interacting through shared environments. The SISE-RCT model is a compartmental susceptible–infectious–susceptible (SIS) model with transmission through environmental (E) compartments and simulated to steady state to approximate a randomized controlled trial (RCT). The black lines denote infection and recovery, the blue lines denote shedding from infectious individuals into environmental compartments, the gray lines denote pick-up of pathogens from the environment by susceptible individuals, and the orange lines denote environmental pathogen decay. S_i and I_i denote susceptible and infectious fraction of the attenuated exposure population, and S_0 and I_0 denote susceptible and infectious fraction of the regular exposure population. E_w, E_f, and E_o denote environmental pathways for water, fomites and hands, and all other pathways. This figure was adapted from Figure 2 of Brouwer et al.[31] In this multi-intervention analysis, we included 15 different attenuated exposure populations alongside the regular exposure population, all interacting through the shared environments.

$$\frac{dI_H}{dt} = \left(\beta_w E_w + \varphi_{\beta_f,H} \times \beta_f E_f + \beta_o E_o\right) S_H - \gamma I_H,$$

$$\frac{dI_N}{dt} = \varphi_{\beta,N} \times \left(\beta_w E_w + \beta_f E_f + \beta_o E_o\right) S_H - \gamma I_H,$$

$$\frac{dI_{WS}}{dt} = \left(\varphi_{\beta_w,W} \times \beta_w E_w + \beta_f E_f + \beta_o E_o\right) S_{WS} - \gamma I_{WS},$$

$$\frac{dI_{WH}}{dt} = \left(\varphi_{\beta_w,W} \times \beta_w E_w + \varphi_{\beta_f,H} \times \beta_f E_f + \beta_o E_o\right) S_{WH} - \gamma I_{WH},$$

$$\frac{dI_{WN}}{dt} = \varphi_{\beta,N} \times \left(\varphi_{\beta_w,W} \times \beta_w E_w + \beta_f E_f + \beta_o E_o\right) S_{WN} - \gamma I_{WN},$$

$$\frac{dI_{SH}}{dt} = \left(\beta_w E_w + \varphi_{\beta_f,H} \times \beta_f E_f + \beta_o E_o\right) S_{SH} - \gamma I_{SH},$$

$$\frac{dI_{SN}}{dt} = \varphi_{\beta,N} \times \left(\beta_w E_w + \beta_f E_f + \beta_o E_o\right) S_{SN} - \gamma I_{SN},$$

$$\frac{dI_{HN}}{dt} = \varphi_{\beta,N} \times \left(\beta_w E_w + \varphi_{\beta_f,H} \times \beta_f E_f + \beta_o E_o\right) S_{HN} - \gamma I_{HN},$$

$$\frac{dI_{WSH}}{dt} = \left(\varphi_{\beta_w,W} \times \beta_w E_w + \varphi_{\beta_f,H} \times \beta_f E_f + \beta_o E_o\right) S_{WSH} - \gamma I_{WSH},$$

$$\frac{dI_{WSN}}{dt} = \varphi_{\beta,N} \times \left(\varphi_{\beta_w,W} \times \beta_w E_w + \beta_f E_f + \beta_o E_o\right) S_{WSN} - \gamma I_{WSN},$$

$$\frac{dI_{WHN}}{dt} = \varphi_{\beta,N} \times \left(\varphi_{\beta_w,W} \times \beta_w E_w + \varphi_{\beta_f,H} \times \beta_f E_f + \beta_o E_o\right) S_{WHN} - \gamma I_{WHN},$$

$$\frac{dI_{SHN}}{dt} = \varphi_{\beta,N} \times \left(\beta_w E_w + \varphi_{\beta_f,H} \times \beta_f E_f + \beta_o E_o\right) S_{SHN} - \gamma I_{SHN},$$

$$\frac{dI_{WSHN}}{dt} = \varphi_{\beta,N} \times \left(\varphi_{\beta_w,W} \times \beta_w E_w + \varphi_{\beta_f,H} \times \beta_f E_f + \beta_o E_o\right) S_{WSH} - \gamma I_{WSH},$$

$$\frac{dE_w}{dt} = \alpha_w \left(\sum_{S \text{ not in } i} I_i + \varphi_{\alpha,S} \sum_{S \text{ in } i} I_i\right) - \xi_w E_w,$$

$$\frac{dE_f}{dt} = \alpha_f \left(\sum_i I_i\right) - \xi_f E_f,$$

$$\frac{dE_o}{dt} = \alpha_o \left(\sum_i I_i\right) - \xi_o E_o. \quad (2)$$

To find the steady state values (denoted by *) for the human compartments in the intervention arm, we set the above equations to 0 and simplified:

$$0 = (R_{0,w}\overline{E}_w + R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_0^* - I_0^*,$$

$$0 = (\varphi_{\beta_w,W} \times R_{0,w}\overline{E}_w + R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_W^* - I_W^*,$$

$$0 = (R_{0,w}\overline{E}_w + R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_S^* - I_S^*,$$

$$0 = (R_{0,w}\overline{E}_w + \varphi_{\beta_f,H} \times R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_H^* - I_H^*,$$

$$0 = \varphi_{\beta,N} \times (R_{0,w}\overline{E}_w + R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_N^* - I_N^*,$$

$$0 = (\varphi_{\beta_w,W} \times R_{0,w}\overline{E}_w + R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_{WS}^* - I_{WS}^*,$$

$$0 = (\varphi_{\beta_w,W} \times R_{0,w}\overline{E}_w + \varphi_{\beta_f,H} \times R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_{WH}^* - I_{WH}^*,$$

$$0 = \varphi_{\beta,N} \times (\varphi_{\beta_w,W} \times R_{0,w}\overline{E}_w + R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_{WN}^* - I_{WN}^*,$$

$$0 = (R_{0,w}\overline{E}_w + \varphi_{\beta_f,H} \times R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_{SH}^* - I_{SH}^*,$$

$$0 = \varphi_{\beta,N} \times (R_{0,w}\overline{E}_w + R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_{SN}^* - I_{SN}^*,$$

$$0 = \varphi_{\beta,N} \times (R_{0,w}\overline{E}_w + \varphi_{\beta_f,H} \times R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_{HN}^* - I_{HN}^*,$$

$$0 = (\varphi_{\beta_w,W} \times R_{0,w}\overline{E}_w + \varphi_{\beta_f,H} \times R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_{WSH}^* - I_{WSH}^*,$$

$$0 = \varphi_{\beta,N} \times (\varphi_{\beta_w,W} \times R_{0,w}\overline{E}_w + R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_{WSN}^* - I_{WSN}^*,$$

$$0 = \varphi_{\beta,N} \times (\varphi_{\beta_w,W} \times R_{0,w}\overline{E}_w + \varphi_{\beta_f,H} \times R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_{WHN}^* - I_{WHN}^*,$$

$$0 = \varphi_{\beta,N} \times (R_{0,w}\overline{E}_w + \varphi_{\beta_f,H} \times R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_{SHN}^* - I_{SHN}^*,$$

$$0 = \varphi_{\beta,N} \times (\varphi_{\beta_w,W} \times R_{0,w}\overline{E}_w + \varphi_{\beta_f,H} \times R_{0,f}\overline{E}_f + R_{0,o}\overline{E}_o)S_{WSHN}^* - I_{WSHN}^*,$$

$$\overline{E}_w = \sum_{S \text{ not in } i} I_i^* + \varphi_{\alpha,S} \sum_{S \text{ in } i} I_i^*,$$

$$\overline{E}_f = \overline{E}_o = \sum_i I_i^*. \quad (3)$$

Here, $R_{0,j} = {}^{\alpha_j\beta_j}/_{\xi_j\gamma}$ is the pathway-specific reproduction number for transmission through environment E_j. The variables $\overline{E}_j = \xi_j E_j^*/\alpha_j$ are conveniently scaled environmental steady states. For this model, the overall basic reproduction number is $R_0 = R_{0,w} + R_{0,f} + R_{0,o}$, denoting the sum of the transmission potential through each pathway in the absence of intervention.

To solve for the steady-state solutions for our 32 state variables (16 exposure groups times two susceptible/infection states), we solve the nonlinear system of equations (Equation 3) subject to the population constraint given in Equation 1. The prevalence of disease in cluster l is denoted $\pi_l^* = \sum I_{i,l}^*$. The prevalence across all clusters in an intervention arm π^* was compared to the prevalence π_c^* in the control arm, and the intervention effectiveness for that arm was defined as $\varepsilon = (\pi_c^* - \pi^*)/\pi_c^*$, namely the fractional reduction in prevalence in the intervention arm relative to the control arm.

In summary, the model included 18 parameters: *a*) the overall basic reproduction number R_0, which defines the transmission potential in the control arm at baseline; *b*) two parameters partitioning R_0 into the strengths of the drinking water $R_{0,w}$, fomite and hands $R_{0,f}$, and all other transmission pathways $R_{0,o}$; *c*) eight relative reproduction numbers accounting for systematic differences in disease pressure over the trial time periods (enrollment, year 1, and year 2) and across arms independently; *d*) the community coverage ω; and *e*) efficacy parameters defining the effect of each intervention (four) or preexisting WASH condition (two) on the transmission pathways the W intervention (chlorination) reduced transmission via the water pathway $\varphi_{\beta_w,W}$, the S intervention (latrine with water seal) reduced shedding into the shared water environment with different efficacy for preexisting conditions $\overline{\varphi}_{\alpha_w,S}$ and the trial intervention $\varphi_{\alpha_w,S}$, the H intervention (handwashing with soap and water) reduced transmission via the fomite pathway with different efficacy for preexisting conditions $\overline{\varphi}_{\beta_f,H}$ and trial intervention $\varphi_{\beta_f,H}$, and the N intervention (nutrition supplementation) reduced susceptibility to all transmission $\varphi_{\beta,N}$). In Equation 3, the basic reproduction number parameters were adjusted by the time and arm-specific and relative basic reproduction numbers corresponding to the cluster being modeled, and the intervention efficacy parameters $\varphi_{\alpha_w,S}$ and $\varphi_{\beta_f,H}$ were replaced by $\overline{\varphi}_{\alpha_w,S}$ and $\overline{\varphi}_{\beta_f,H}$ in clusters without the S and H interventions, respectively, and at enrollment.

When solving for the steady state of these equations for a given cluster in a given time period, we used the distribution of interventions and preexisting WASH conditions ρ recorded in the data for those participants and assumed that participants not in the study had the same distribution of preexisting conditions as the control arm participants ρ_0. We solved this system using the `nleqslv` package in R (v4.4).

To fit the model to the trial data, we employed a hybrid approach that combined Bayesian sampling-importance resampling with maximum-likelihood estimation framework to obtain 50,000 parameter combinations that represented a good fit to the diarrheal outcomes of each participant using a Bernoulli statistical likelihood.[31] Specifically, we defined $\pi_k(\theta)$ to be the modeled (cluster- and period-specific) prevalence corresponding to observation k (corresponding to a participant at a time point) as a function of the eighteen parameters θ, and we let x_k be the indicator of diarrhea for that observation. The Bernoulli likelihood was then $L(\theta) = \prod_k \left((\pi_k(\theta))^{x_k} (1 - \pi_k(\theta))^{1-x_k} \right)$. We designated R_0 and the eight arm- and time-specific reproduction numbers as the parameters to be estimated and the rest as parameters to be sampled. The sampled parameters were collectively sampled 50,000 times from [0,1] (except for community coverage, which was sampled between 1×10^{-5} and 0.2) using a Sobol sample, creating a joint uniform prior distribution. For each of these samples, we found the best fit values of each of the estimated parameters by minimizing $-\log(L(\theta))$ using a nonlinear minimization algorithm. We then calculated sampling-importance resampling weights by converting the best-fit likelihood of each sample to a normalized probability. We then resampled, with replacement, from our initial 50,000 parameter combinations, using these goodness-of-fit sampling weights, creating a joint posterior distribution. Additional details may be found in Brouwer et al.,[31] and the associated code and parameter combinations are given in the supplemental material and in the public repository linked in the data availability statement.

WASH-B Bangladesh Counterfactual Analysis

We conducted two types of counterfactual analyses. First, we estimated the counterfactual intervention effectiveness in each arm across a range of each of the WASH factors starting from the scenario based on the median value of each parameter (Table 1). Using the median values resulted in a fit close to the best-fit and was more representative of the parameter distributions than the specific best-fit parameter set. Because we used the actual preexisting WASH conditions and intervention compliance recorded for each individual in the trial, there was not a well-defined way to continuously scale these two factors. So, we only compared the actual simulation to a "no preexisting conditions" and "full compliance" counterfactual, respectively, for these factors.

Second, because we did not know that the median values of the parameters in the scenario investigated in the first counterfactual analysis were accurate, we also considered the distribution of changes in intervention effectiveness when each counterfactual scenario (Table 2) was applied to the distribution of samples that fit the original data well. To account for the uncertainty in the parameters underlying the actual intervention outcomes, for each of the 50,000 parameter sets m identified by fitting the model to WASH-B Bangladesh, we defined the corresponding original scenario matching the WASH-B Bangladesh trial outcomes and the corresponding intervention effectiveness ε_m^0. Because we accounted for uncertainty across these 50,000 parameter sets, it was not possible to succinctly capture changes as we continuously varied the factors. Thus, we considered six specific counterfactual scenarios, detailed in Table 2. Any parameter sets that eliminated disease in the control arm in a counterfactual simulation were censored from the results, as they did not provide information on intervention effectiveness.

The main outcome of a counterfactual simulation was the (absolute) change intervention effectiveness compared to the original scenario, namely $\varepsilon_m^{**} - \varepsilon_m^0$, where ε_m^{**} is the intervention effectiveness in the given counterfactual scenario for the mth parameter set. We used absolute change rather than percentage change because absolute change, unlike percent change, is bounded between -100 and 100 percentage points. The intervention was more effective (i.e., a greater reduction in diarrheal prevalence in the intervention arm compared to the control arm) in the counterfactual scenario than the original scenario when the change was positive. To assess whether the intervention factors modified the effect of community coverage on intervention effectiveness in the counterfactual scenarios, we determined how the effect of the counterfactual depended on quantiles of the values of the other WASH factors.

The counterfactuals scenarios are not intended to be "plausible" for some specific, real-world changes. Indeed, changing the contextual factors of the preexisting WASH conditions and baseline disease prevalence would not be possible. Instead, we can imagine these counterfactuals represent running the same trial in a different location to assess what the results would have been. The intervenable fraction is also not changeable for a given intervention (and underlying set of pathogens) but could be changed by adding additional intervention aspects to reduce transmission along other pathways. More broadly, we believe that investigating a broad range of counterfactual scenarios improves our understanding of the disease–intervention system so that more effective interventions may be designed in the future.

Results

Calibrating to the WASH-B Bangladesh Trial

The hybrid sampling-importance resampling and estimation framework resulted in 50,000 parameter combinations, representing 3,774 unique parameter combinations with varying frequency. Please note that these parameters sets are similar to but not exactly the same as in Brouwer et al.,[31] as they include a small code correction and use the updated computational approach that solves for the steady state values directly. The parameter sets and code are given in the supplemental material. The fit to the data is given in Figure S1 (Excel Table S1), and the distributions of parameters are given in Figures S2–S5 (Excel Tables S2–S5).

WASH-B Bangladesh Counterfactual Analysis from the Median Parameters

At the median model parameter values (Table 1), the effectiveness of the intervention was 8.5% in the W arm, 40.8% in the S arm, 37.2% in the H arm, 32.1% in the WSH arm, 35.0% in N

Table 2. WASH Benefits Bangladesh counterfactual scenarios and implementations.

Category	Definition	What would have happened if...	Implementation
WASH conditions	Quality of WASH infrastructure at baseline	... no households had preexisting WASH conditions substantively equivalent to the intervention.	Preexisting conditions were removed from individuals not in the corresponding intervention arms. [Setting ρ_0^{**} to the vector $(1, 0, \ldots, 0)$].
Compliance	The extent to which individuals assigned to an intervention received it (fidelity) and used it (adherence)	... all households assigned an intervention received and used it.	All individuals in each intervention arm were modeled as using the intervention (adjusting ρ^{**} appropriately, e.g., moving the fraction of the population from S to HS in the hygiene arm).
Disease conditions	Disease prevalence at baseline in the absence of preexisting WASH conditions	... the disease pressure was greater.	The basic reproduction number is increased such that the baseline prevalence in the absence of preexisting WASH conditions is doubled. (Optimization was used to determine the appropriate value of R_0^{**} for each parameter set.)
Intervenable fraction	Whether there are transmission pathways that are not affected by the intervention	... more of transmission was along pathways that could be intervened on.	The strength of the other pathway is reduced by 50% and replaced proportionally by the water and fomite pathways. [$R_{0,w}^{**} = R_{0,w} + \frac{1}{2}R_{0,o} \times R_{0,w}/(R_{0,w}+R_{0,f})$, $R_{0,f}^{**} = R_{0,f} + \frac{1}{2}R_{0,o} \times R_{0,f}/(R_{0,w}+R_{0,f})$, $R_{0,o}^{**} = \frac{1}{2}R_{0,o}$]
Efficacy	The extent to which using the intervention reduced transmission along relevant pathways	... the interventions provided a greater reduction in transmission.	The strength of the reduction in transmission from each intervention (and corresponding preexisting condition) is doubled ($\varphi^{**} = \min(2\varphi, 1)$)
Community coverage	The fraction of the at-risk population in a cluster that was provided the intervention	... a different fraction of the population was provided the intervention.	Study coverage is 20%, ..., 90%, 100%. ($\omega^{**} = 0.2, \ldots, 1.0$)

Note: H, hygiene; N, nutrition; S, sanitation; W, water; WASH, water, sanitation, and hygiene; **, parameters in the counterfactual simulation.

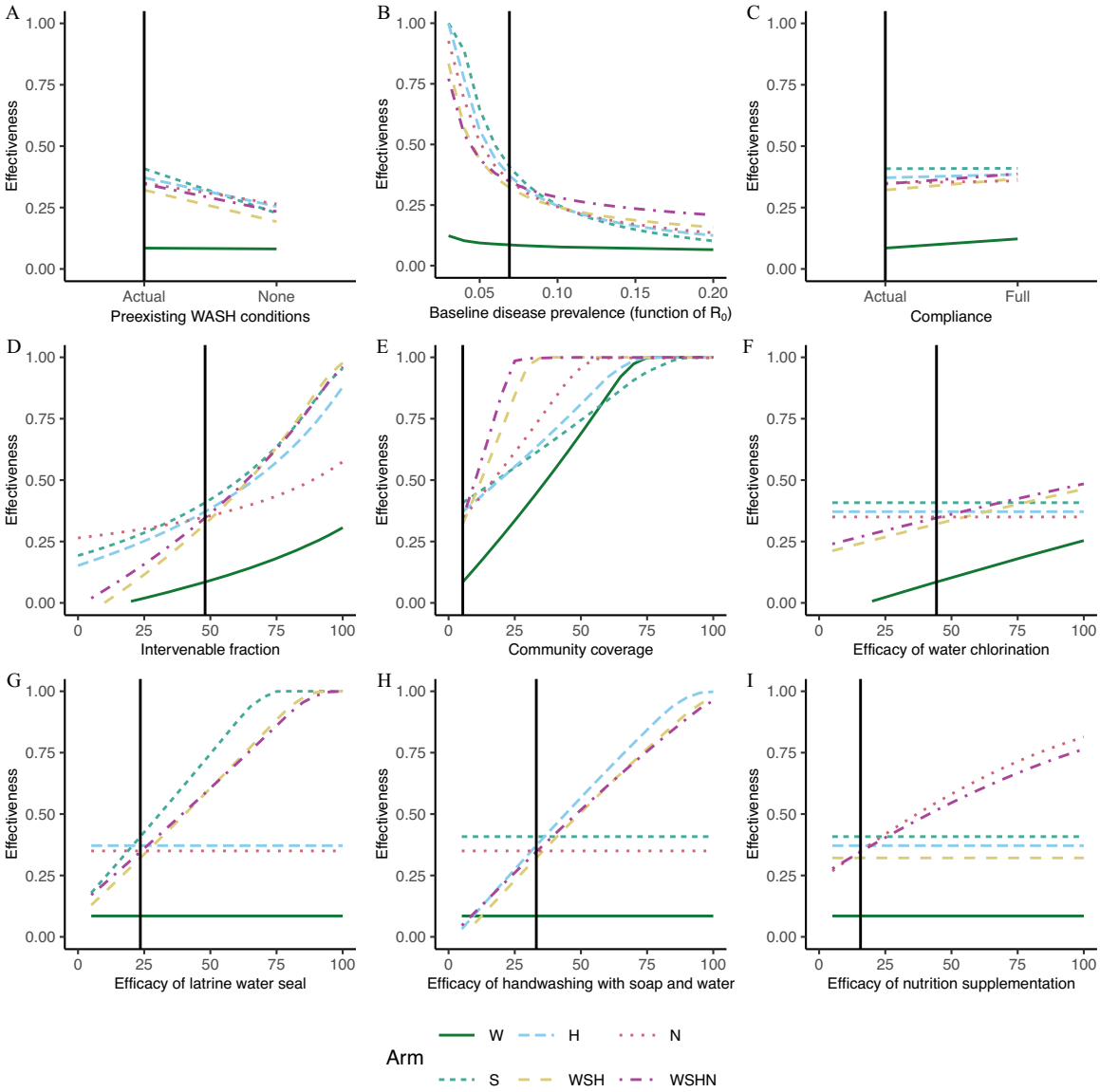

Figure 2. Intervention effectiveness as a function of WASH intervention factors estimated for the WASH Benefits Bangladesh trial. The SISE-RCT model is a compartmental susceptible–infectious–susceptible (SIS) model with transmission through environmental (E) compartments and simulated to steady state to approximate a randomized controlled trial (RCT). Effectiveness is defined as 1 minus the relative prevalence of diarrhea in the intervention arm compared to the control arm. The model was simulated at the median values of the model parameters when fit to the WASH Benefits Bangladesh trial and across ranges of counterfactual values of six contextual and intervention WASH factors. The six WASH factors are (A) preexisting WASH conditions (fraction of individuals not enrolled in the intervention arm that are using preexisting WASH infrastructure), (B) baseline disease prevalence (a function of the basic reproduction number R_0), (C) compliance (fraction of individuals enrolled in the intervention arm that are using the intervention), (D) intervenable fraction of transmission (how much of the transmission could be prevented in a perfect intervention), (E) the community coverage fraction (fraction of the population enrolled in the trial), and (F–I) the intervention efficacy (fraction reduction in transmission or shedding when using the intervention) of each intervention. Please note that the *x*-axes for panels A and C are dichotomous; the lines are included to aid with visual comparison only and do not imply a continuous scale. The data underlying Figures 2A–2I are provided in Excel Tables S6–S14. Note: WASH, water, sanitation, & hygiene.

arm, and 34.6% in the WSHN arm, reflecting the results of the WASH-B Bangladesh trial. (Note, these values are the effectiveness of the intervention at the median parameter values, not the median effectiveness across all resampled parameter sets, which is discussed below). We estimated that removing all preexisting sanitation and hygiene infrastructure would have resulted in a modest reduction in intervention efficacy in all arms except for W, where the reduction was negligible (Figure 2A; Excel Table S6). Increasing baseline disease prevalence (by increasing the R_0 parameter) nonlinearly decreased intervention effectiveness in all arms, with decreasing reductions in effectiveness as baseline prevalence increased (Figure 2B; Excel Table S7). We estimated that there would be negligible-to-modest improvements in intervention effectiveness if there was full compliance (Figure 2C; Excel Table S8). Increasing the intervenable fraction (by reducing the strength of the "other" pathway and proportionally increasing the strength of the water and fomite and hands pathways while keeping the overall R_0 constant) increasingly improved the intervention effectiveness (Figure 2D; Excel Table S9), with the WSH and WSHN interventions nearly achieving disease elimination if transmission were 100% intervenable. Increasing community coverage increased intervention effectiveness approximately linearly, with each intervention achieving disease elimination at a different level of community coverage (Figure 2E; Excel

Table 3. Median intervention effectiveness and median percentage point change in intervention effectiveness in each intervention arm for each counterfactual scenario compared to the original scenario of the WASH benefits Bangladesh trial.

	W		S		H		WSH		N		WSHN	
	ε	Δε	ε	Δε	ε	Δε	ε	Δε	ε	Δε	ε	Δε
Original scenario	8.1%	—	36.3%	—	33.0%	—	30.2%	—	33.9%	—	34.5%	—
No WASH baseline conditions	8.0%	−0.2%	21.7%	−14.6%	24.6%	−8.6%	20.6%	−9.5%	26.5%	−7.3%	25.7%	−8.4%
Double baseline disease prevalence	6.8%	−1.3%	14.7%	−21.6%	15.7%	−17.5%	18.6%	−11.9%	17.7%	−16.0%	24.1%	−10.3%
Full compliance	11.6%	+3.6%	36.4%	+0.1%	34.2%	+1.1%	34.7%	+4.4%	34.7%	+0.9%	38.6%	+4.1%
Half of other pathway transmission can be intervened on	14.2%	+6.0%	48.4%	+11.8%	43.7%	+10.6%	50.8%	+20.1%	37.8%	+3.8%	53.0%	+18.2%
Double efficacy of chlorination	15.4%	+7.1%	—	—	—	—	36.4%	+6.1%	—	—	40.6%	+5.9%
Double efficacy of latrine water seal	—	—	55.4%	+18.9%	—	—	46.0%	+15.7%	—	—	48.9%	+14.2%
Double efficacy of handwashing	—	—	—	—	54.6%	+21.3%	50.2%	+19.8%	—	—	52.8%	+18.3%
Double efficacy of nutrition	—	—	—	—	—	—	—	—	45.3%	+11.3%	44.3%	+10.1%
Increase community coverage to 20%	22.9%	+14.6%	43.3%	+6.8%	41.4%	+8.3%	63.8%	+34.0%	49.2%	+15.3%	79.6%	+45.5%

Note: Intervention effectiveness (ε) in intervention effectiveness is 1 minus the relative risk of diarrhea in an intervention arm vs. the control arm in each scenario, expressed as a percentage. The column Δε gives the median change in intervention effectiveness in percentage points (not the change in median intervention effectiveness); a negative number reflects a decrease in intervention effectiveness. These values come from a counterfactual analysis (Table 2) of the WASH benefits Bangladesh trial using a compartmental susceptible–infectious–susceptible (SIS) model with transmission through environmental (E) compartments and simulated to steady state to approximate a randomized controlled trial. H, hygiene; N, nutrition; S, sanitation; W, water; WASH, water, sanitation, and hygiene.

Table S10; W: 75%, S: 90%, H: 75%, WSH: 35%, N: 55%, WSHN: 30%). Increasing intervention efficacy approximately linearly increased intervention effectiveness in the corresponding arms (Figure 2F–I; Excel Tables S11–S14). Increasing efficacy of the S and H interventions to 100% resulted in approximate disease elimination in the corresponding arms, but elimination would not have been achieved by increasing the efficacy of the W and N interventions.

WASH-B Bangladesh Counterfactual Analysis Accounting for Parameter Uncertainty

The median baseline disease prevalence in the original scenario was 7.1% (range, 5.9–8.2%), decreasing to 5.7% (range, 5.2–6.3%) for years 1 and 2 of the study (Figure S1; Excel Table S1). The median intervention effectiveness was 8.1% in the W arm, 36.3% in the S arm, 33.0% in the H arm, 30.2% in the WSH arm, 33.9% in N arm, and 34.5% in the WSHN arm (Table 3). The percentage point change varied across arms in each counterfactual scenario: Figure 3 shows the distribution of percentage point change in intervention effectiveness over the 50,000 parameter sets for each arm and counterfactual scenario, and Table 3 gives the median change.

Eliminate preexisting WASH conditions. We found that implementing the interventions in a community with no handwashing stations with soap and water or latrines with water seals (at enrollment) would have likely resulted in less effective interventions compared to the actual community's higher baseline WASH conditions (e.g., 9.5 percentage points less in the WSH arm) (Figure 3A; Excel Table S15). The W arm was the exception because it had lower effectiveness in the original scenario. The uncertainty in change in intervention effectiveness in each arm was largely driven by uncertainty in what the baseline disease prevalence would have been in the counterfactual scenario (median, 8.9%; range, 6.4–23.1%).

Double baseline disease prevalence. A higher transmission potential corresponding to a doubling of the baseline diarrheal disease prevalence (doubled enrollment median = 14.2% vs. true enrollment median = 7.1%) would also have resulted in less-effective interventions compared to the true enrollment diarrheal disease prevalence (e.g., 11.9 percentage points less in the WSH arm) (Figure 3B; Excel Table S16). As above, the W arm is the exception because it had lower effectiveness in the original scenario.

Full compliance. The impact of increasing intervention adherence was negligible-to-modest (e.g., 4.4 percentage points more in the WSH arm) (Figure 3C; Excel Table S17).

Half of the "other transmission" pathway can be intervened on. We found that intervention effectiveness could have been greater if more of the total disease transmission was via the water and fomite pathways rather than through pathways that were not intervened on (e.g., 20.1 percentage points more in the WSH arm) (Figure 3D; Excel Table S18). There was potential for a substantial increase in intervention effectiveness as indicated by the distribution of the individual simulation outcomes, but the median impact was modest, with a <25 percentage point increase in effectiveness in the multi-intervention arms and a <15 percentage point increase in the single-intervention arms (Table 3). The uncertainty in the potential impact was largely driven by uncertainty in how much of the disease transmission was through other pathways in the original scenario.

Double intervention efficacy. We assessed the impact of increasing efficacy—defined as increasing the reduction of transmission along the relevant pathway(s)—of the four interventions. We found that in each of these increased efficacy scenarios, substantial increases in intervention efficacy could have improved intervention effectiveness in the corresponding arms (Figure 3E–H; Excel Tables S19–S22), with median improvements between 5 and 20 percentage points.

Increase community coverage. The median estimated community coverage in the trial was 5.4%, but this estimate was highly uncertain, ranging from nearly 0% to 20% (Figure S5; Excel Table S5). The counterfactual scenario of 20% community coverage was associated with the greatest median increase in intervention effectiveness (among all households now covered by the intervention) of any of the considered counterfactual scenarios (e.g., 34.0 and 45.5 percentage points more in the WSH and WSHN arms) (Figure 4A; Excel Table S23). Effect modification of the effect of increased coverage by the other factors was present if the effect of increased coverage depended on the quintiles of the WASH factor (Figure 4B–H; Excel Tables S24–S30). Note that when looking at quintiles of one factor, the values of the other factors may not be evenly distributed across the quintiles if values of the factors are correlated. We found that the increased intervention effectiveness with increased community coverage in the W, S, WSH, and WSHN intervention arms depended partly on the strength of transmission via the water pathway (Figure 4B; Excel Table S24). The increases in intervention effectiveness in these arms could only reach their full potential if the strength of the water pathway were

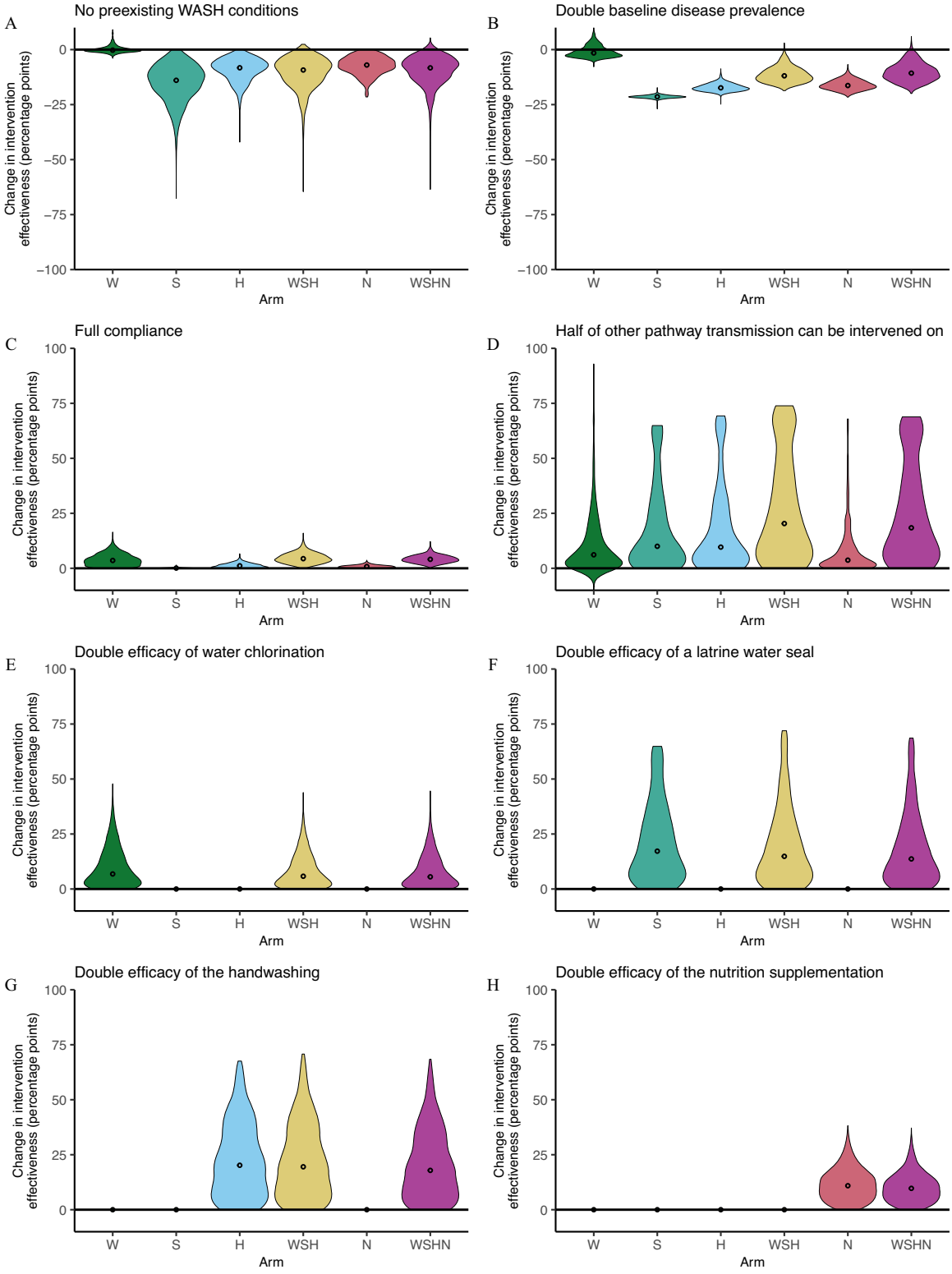

Figure 3. Percentage point change in intervention effectiveness compared to the original scenario in each counterfactual scenario estimated for the WASH Benefits Bangladesh trial. The SISE-RCT model is a compartmental susceptible–infectious–susceptible (SIS) model with transmission through environmental (E) compartments and simulated to steady state to approximate a randomized controlled trial (RCT). Here, we applied it to data from the WASH Benefits Bangladesh trial, selecting 50,000 parameter sets consistent with the trial outcomes. We simulated each parameter set under each counterfactual scenario (Table 2). The violin plots give the distribution of values across the 50,000 simulations, with median points. The underlying data are provided in Excel Tables S15–S22. Note: H, hygiene; N, nutrition; S, sanitation; W, water; WASH, water, sanitation, and hygiene.

high. A similar, but more modest effect was seen for the H arm and the strength of the fomites and hands pathway (Figure 4C; Excel Table S25). The greatest overall effect modifier of the impact of increased coverage on intervention effectiveness was the strength of the "other" transmission pathways (i.e., the intervenable fraction) (Figure 4D, Excel Table S26). When the strength of other

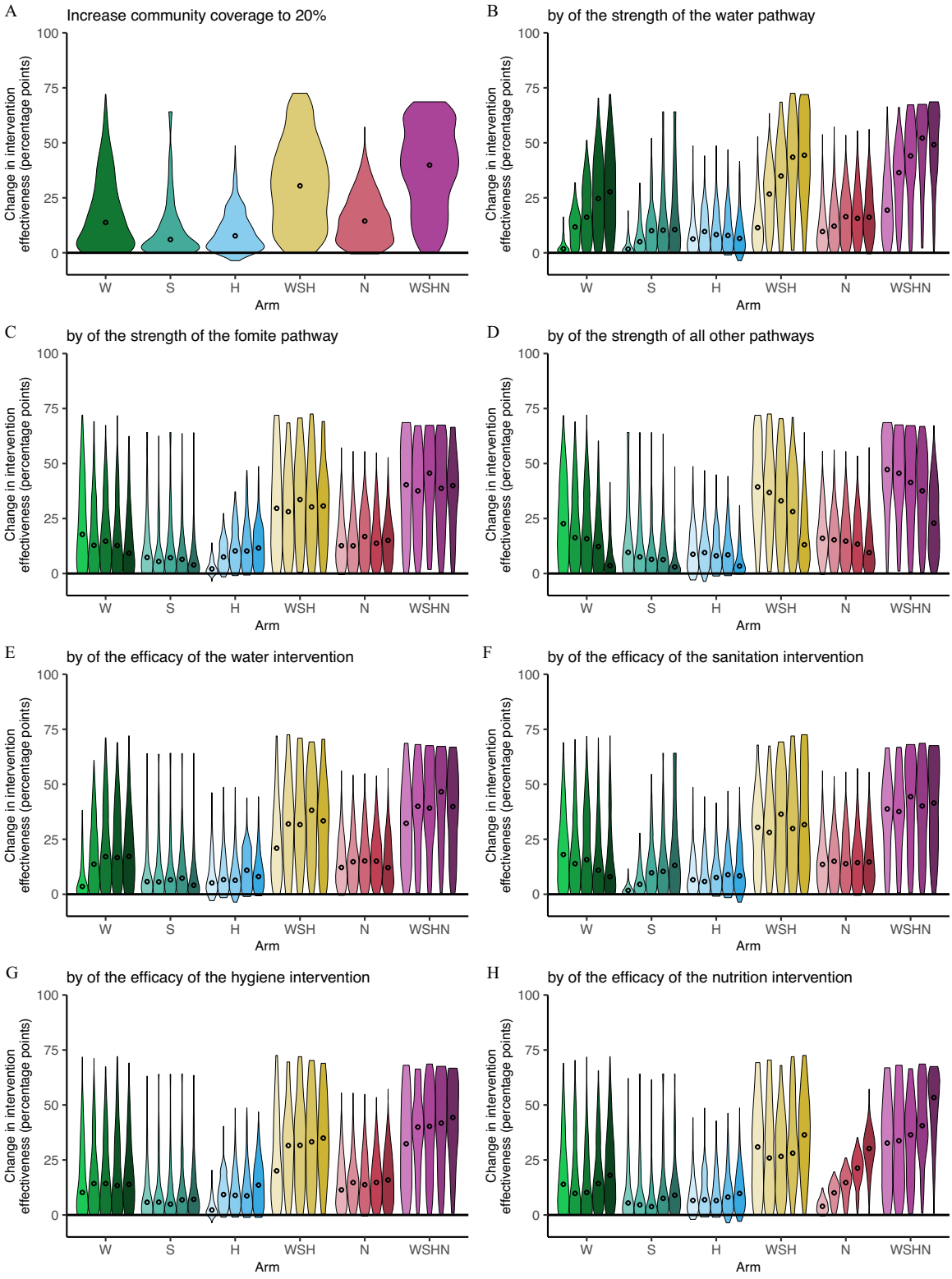

Figure 4. Percentage point change in intervention effectiveness compared to the original scenario in the 20% community coverage counterfactual scenario (A) overall and (B–H) considering other parameters as potential effect modifiers estimated for the WASH Benefits Bangladesh trial. The SISE-RCT model is a compartmental susceptible–infectious–susceptible (SIS) model with transmission through environmental (E) compartments and simulated to steady state to approximate a randomized controlled trial (RCT). Here, we applied it to data from the WASH Benefits Bangladesh trial, selecting 50,000 parameter sets consistent with the trial outcomes. We simulated each parameter set under the 20% community coverage counterfactual scenario (Table 2). The violin plots give the distribution of values across the 50,000 simulations, with median points. In plots B–H, the five violin plots give the distributions of the intervention effectiveness across quintiles, from lowest to highest, of the listed potential effect modifier. The underlying data are provided in Excel Tables S23–S30. Note: H, hygiene; N, nutrition; S, sanitation; W, water.

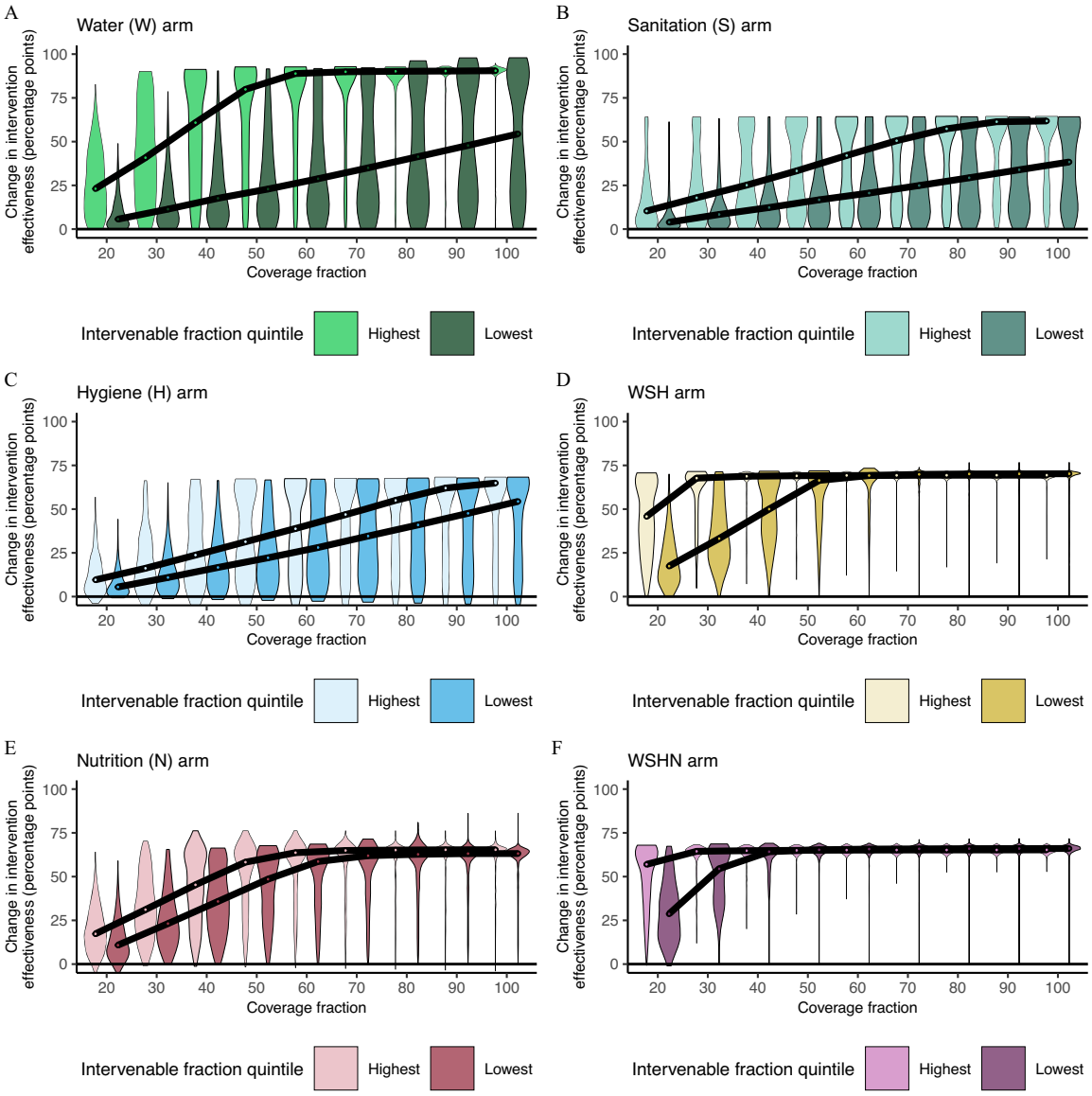

Figure 5. Percentage point change in intervention effectiveness compared to the original scenario for a range of counterfactual community coverage values in each arm estimated for the WASH Benefits Bangladesh trial for the lowest and highest quintiles of intervenable fraction. The SISE-RCT model is a compartmental susceptible–infectious–susceptible (SIS) model with transmission through environmental (E) compartments and simulated to steady state to approximate a randomized controlled trial (RCT). Here, we applied it to data from the WASH Benefits Bangladesh trial, selecting 50,000 parameter sets consistent with the trial outcomes. We simulated each parameter set for community coverage counterfactual scenarios ranging from 20% to 100% (Table 2). The violin plots give the distribution of values across the simulations, with median points and a line connecting the medians, for highest (dark) and lowest (light) quintiles of the intervenable fraction, i.e., the fraction of transmission that the interventions could directly act on. The underlying data are provided in Excel Tables S31–S36. Note: H, hygiene; N, nutrition; S, sanitation; W, water; WASH, water, sanitation, and hygiene.

pathways was high, increasing coverage had less of an impact. Intervention efficacy also modified the impact of increased coverage but only in the intervention arms with those interventions (Figure 4E–H; Excel Tables S27–S30).

To further understand the joint impact of community coverage and the intervenable fraction (i.e., the strength of the other transmission pathway), we plotted the intervention effectiveness as a function of increased coverage for the highest and lowest quintiles of intervention completeness (Figure 5; Excel Tables S32–S36). The impact of increased coverage on intervention effectiveness depended on the intervenable fraction most strongly for the W, WSH, and WSHN arms, moderately for the S arm, and little for the H and N arms. For example, in the W arm, increasing community coverage to 50% resulted in a median increase of 80 percentage points for samples with the highest intervenable fractions but only 23 percentage points for samples with the lowest intervenable fractions. In contrast, in the H arm, increasing community coverage to 50% resulted in a median increase of 31 percentage points for samples with the highest intervenable fractions compared to only 22 percentage points for samples with the lowest intervenable fractions. [Note that the fact that intervenable fraction was relevant for the N arm at all is because the intervenable fraction is not independent of the other parameters in the original parameter sets (provided in the supplemental material).]

Discussion

Our model-based analysis used counterfactual simulations to generalize the results of a WASH intervention trial and develop guidance for policymakers and researchers. Our first finding was that

increasing community coverage would have led to the most substantial reduction in disease among people receiving interventions. Second, we found that intervention completeness (i.e., the fraction of disease transmission along pathways that were intervened on) was an important effect modifier of the impact of community coverage on intervention effectiveness, with the impact of increased community coverage enhanced when interventions covered a larger fraction of transmission. Third, our work suggests that interventions are likely to be more effective when disease burden is low. Finally, we found that multifaceted WASH interventions (WSH) added value over single component interventions (W, S, or H). Each of these findings suggest a path forward for policy and program recommendations for WASH investments and demonstrates how transmission models can be used to design the next generation of WASH interventions and set location-specific programmatic targets.

The importance of ensuring high community coverage to address health outcomes has been highlighted for multiple interventions, including latrines,[30,34] bed nets,[35] and chemotherapy for helminths,[36] among others. Further work is needed to improve our measures of indirect and direct intervention effects[30,37] to better determine sanitation targets. Our findings support the call for systems-level WASH provisioning and improved universal access, underscoring the fundamental push to achieve the 2030 sustainable development targets.[38]

Our finding that the intervenable fraction (completeness) was an important effect modifier emphasizes the need to better understand the sources of exposure not impacted by traditional WASH interventions. For example, contamination of food outside the home or from flies or exposure to feces from animals living near or inside the home may not be reduced by water quality or latrine interventions.[39–41] Capturing and reducing transmission through additional targeted interventions would increase the fraction of transmission intervened on and, thereby, make increased community coverage even more effective.

Low diarrheal prevalence makes it more difficult to observe a statistically significant reduction in diarrhea.[15] However, from a mechanistic perspective, we found that intervention effectiveness would have been lower had the background disease pressure in the community been higher (i.e., higher baseline disease prevalence) because individual-level interventions can be overwhelmed by higher disease pressure from the community, including those not covered by the intervention. This finding is supported by the outcomes of the WASH-B Kenya trial, which had higher disease prevalence (27% in the control arm) and no significant intervention effects on diarrheal prevelance,[16] and is consistent with previous literature that has shown that nonpharmaceutical interventions are more effective for less transmissible pathogens or when the population has a higher degree of population immunity.[42] This is not to say that individual improvements would have no effect but that the effects are reduced if disease pressure in the rest of the community is not also addressed.

Similarly, many have suggested that when preexisting WASH conditions are relatively high, interventions do not provide a substantial improvement in efficacy and thus health outcomes.[19,20,23,43] However, from the transmission system perspective reflected by our results, if the preexisting WASH conditions (particularly among those not covered by the intervention) were poorer, the community disease pressure would be greater. Thus, it would be more difficult to protect study participants from infection, even if the people covered by the intervention had a greater improvement in protection. We expect that diarrheal prevalence is not independent of preexisting WASH conditions or the efficacy of those conditions, and each of these factors is likely correlated with socioeconomic conditions. Our modeling approach accounts for these correlations so that we can produce unbiased predictions of how an intervention is likely to perform in any given context. This fact highlights an important strength of modeling in both trial design and in the generalization of trial results from one context to another.

Because enteric pathogens can exploit multiple transmission pathways, many studies have tried to determine whether combined WASH interventions (WSH) are more effective than single interventions (W, S, or H).[33,44] Whether or not there is an additional effect of combined interventions depends on whether the interventions are complementary, that is, whether they each block some of the transmission that the other interventions would not have blocked.[45] This complementarity is an assumption in our transmission model framework (as each intervention affects different parts of the disease system), and because the model can fit the data, we find that complementarity is consistent with the observed trial results.[31] Other modeling and empirical studies support that WASH interventions can complement each other or even potentially be synergistic.[46,47] In this work, we found that the combined interventions could have a greater effect than the individual interventions but that the effects were generally subadditive, meaning that the effectiveness of the combined WSH intervention was less than the sum of its parts (Table 3). Nevertheless, combined interventions offer a substantially better chance of disease elimination, especially at higher coverage levels (Figure 5).

One challenge that WASH RCTs often face is achieving high compliance through both high fidelity (providing the interventions as planned) and high adherence of participants to the use of the intervention. In WASH-B Bangladesh, the compliance to each component of the intervention was high, generally above 80% in each arm in both follow-up years.[15,32] Accordingly, our full compliance counterfactual was limited in the impact it could detect.

The strength of our approach is underscored by the rich and high-quality data collected by the WASH-B Bangladesh trial (and other RCTs) and in our transmission model framework capturing relative disease prevalence. RCTs provide the gold standard of evidence about intervention effectiveness in a specific context, and our approach allows us to generalize RCT results to other contexts, providing a tool for powerful policy and programmatic guidance. The SISE-RCT model can be customized for local contexts and interventions and then used to support local decision making (e.g., to determine whether to invest in community coverage vs. intervention efficacy). Future work may also develop recommendations for achieving elimination while minimizing costs.

One limitation of our study is the high uncertainty in many of the model parameters, especially the intervenable fraction, which propagates into the counterfactual scenarios. These uncertainties stem from potential trade-offs in the model, e.g., a low intervenable fraction and a low intervention efficacy may have similar effects on intervention effectiveness. Fortunately, our framework has the potential to incorporate additional information about parameters like the intervenable fraction and efficacy through our Bayesian sampling-importance resampling approach, allowing us to tailor projections of intervention effectiveness to specific parameter regions based on additional information (e.g., if we knew that chlorination efficacy was above 75%). One limitation of the data was the inability to distinguish whether nontarget children were members of the same household as the target child or not, which introduced misspecification into our classification of W and H exposures, likely attenuating the efficacy estimates for those interventions. Also, we accounted for changes in disease pressure between, but not within, survey periods; future work may more directly address seasonal changes in disease pressure and even pathway strength as a function of precipitation, seasonal flooding, etc. Another data limitation is that we did not have information on pathogen-specific infection. Different pathogens exploit different

transmission pathways to different degrees and are differentially affected by different types of interventions (e.g., chlorine is typically less effective against protozoa than bacteria and viruses). The parameters used in our model represent averages over the local pathogen distribution. Other contexts with different pathogen distributions[7] would have different results. We propose that applying our models to RCTs with pathogen infection outcomes would allow for a better understanding of pathogen-specific intervenable fractions and intervention efficacies, which could then be combined to make predictions for new locations with a given pathogen profile. As microarray platforms that provide pathogen diagnostic information become cheaper, we predict that it will become more feasible to collect pathogen-specific data.

Our results also do not directly address some aspects of the United Nations' Sustainable Development Goals (SDG) Target 6.2.[38] For example, the sanitation arm did not move households from no or basic sanitation to improved sanitation (as defined by the Joint Monitoring Program). So, the "sanitation" intervention outcomes that we estimated may not directly correspond to the policy-relevant changes required to meet SDG targets. Likewise, the "water" intervention focused on water quality improvements (chlorination) but not water quantity. None of these issues are limitations of our modeling framework; rather, they are limitations of our specific application to the WASH-B Bangladesh trial. Applying our methods across other trial datasets could address these limitations by allowing for modeling of other—and perhaps more policy-relevant—WASH exposure parameters.

Our work contributes to the robust discussion[19–25,48] about the future directions of WASH research and programming, and our modeling approach is well-suited to reevaluating current evidence during the "pause for reflection" recommended by a consensus of WASH researchers.[20] This consensus group said that "the lesson perhaps lies in not seeking to attribute benefits to individual WASH factors but in that the public health dividends are paid when comprehensive services are in place." Our work underscores this conclusion, not only by emphasizing the importance of coverage and completeness of interventions, but also in its rejection of the hypotheses that greater effectiveness might be found in areas with greater disease prevalence or lower preexisting WASH infrastructure. Indeed, our findings suggest that the effect of individual-level WASH improvements will be reduced more the further the community is from achieving the coverage needed for herd protection. Accordingly, this analysis provides further evidence supporting community-level interventions seeking to achieve herd protection through high community coverage. More broadly, our work highlights the challenges of focusing on RCTs alone, as their results are difficult to generalize to other contexts. Ultimately, the WASH community will benefit from the integration of practitioners with local experience, trialists with the experience in designing high-quality studies, and modelers who can project potential study outcomes.

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J.N.S.E., M.C.E., M.C.F., and A.F.B. conceived of the study. J.N.S.E. and M.C.F. secured funding for the study. A.F.B., M.C.E., and J.N.S.E. developed the model. A.F.B. wrote and implemented the software code, completed formal analysis and visualization, and curated the data and code. M.H.Z. and A.N.M.K. validated the software code. A.F.B. wrote the original draft with input from J.N.S.E. and M.C.F. B.F.A., S.A., J.B.-C., J.M.C., A.E., S.P.L., A.J.P., and M.R. contributed equally by aiding in interpretation of the results and providing their expertise in the WASH Benefits trials. All authors reviewed and edited the manuscript. All authors had full access to all study data.

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The WASH Benefits Bangladesh data is publicly available at https://osf.io/tprw2/. The data and code underlying the results of this paper are available at https://doi.org/10.5281/zenodo.10950560 and are also included as supplemental material. Data underlying each of the figures is given in the Excel spreadsheet supplement.

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