Waterborne, abiotic and other indirectly transmitted (W.A.I.T.) infections are defined by the dynamics of free-living pathogens and environmental reservoirs

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***Abstract*— While the ecology of infectious disease is a rich field with decades worth of empirical evidence and theory, there are aspects that remain relatively under-examined. One such example is the epidemiological relevance of the free-living survival stage of certain pathogens, and especially ones transmitted through an environmental intermediate reservoir rather than directly between individuals. In this study, we use methods from mathematical epidemiology to examine epidemics where the spread of disease includes a dynamic free-living pathogen stage and transmission through an environmental intermediate—the waterborne, abiotic and other indirectly transmitted (W.A.I.T.) infection framework. To demonstrate this, we model two very different disease scenarios: cholera in a densely populated setting with limited access to clean drinking water and hepatitis C virus in an urban setting of injection-drug users. Using these two exemplars, we show that the W.A.I.T. model fosters an appreciation for the centrality of the environmental reservoir in driving many epidemics, and provides a way to simulate potential intervention strategies.**

I. INTRODUCTION

Ecology and evolutionary biology have provided a theoretical basis for understanding how the interaction between pathogens and their environment shapes epidemics. When combined with quantitative modeling methods, it offers a full systems perspective that has helped to characterize the the actors, forces and interactions that create infectious diseases [1]–[9]. Classically, the pathogen-host interaction is the presumptive central determinant of infectious disease, and consequently, the focus of modeling efforts: understand it, model it carefully, and one gains a picture for how epidemics arise and persist.

These methods have been successful in balancing simplicity with generality, and have spawned different classes of models, summarized both in terms of the particular mathematical instruments applied (e.g. discrete-time, continuous models, network models, etc) and the particular biologies of host-pathogen systems (e.g. sexually-transmitted, vector-borne disease, food-borne pathogen, etc) [5], [6]. These methods have been effective in many cases, supported by dozens of examples where they have captured the essential character or dynamics of an epidemic [6], [8]. While these existing classifications have served an effective organizational and pedagogical purpose, there remains room for growth in how we translate certain epidemic phenomenon into theoretical formalism.

One disease-related concept that has been the object of recent inquiry involves infections transmitted through an indirect interaction between hosts and some surface-intermediate where the pathogen lives freely and independently of a host [10]–[26]. Much of this research has been concentrated on fomite, aerosol and airborne-transmitted viruses [10], [11], [13], [14], [16], [19], [21], waterborne infections [12], [17], [22], [25], [27]–[31], or has explored indirectly-transmitted infections in purely theoretical terms [15], [20], [23]. We offer that these are all—across pathogen types and settings—individual examples of a broader phenomenon that would benefit from more holistic and rigorous description. Such a treatment should include, but not be relegated to, diseases of the waterborne and viral contexts and should specifically consider how the environment itself is a dynamic property.

In this study, we develop the "waterborne, abiotic and other indirectly transmitted" (W.A.I.T. or WAIT) paradigm, a generalized framework for understanding pathogens with a free-living survival phase, indirectly transmitted through an environmental reservoir intermediate. As the WAIT perspective specifically focuses on dynamic properties of the environment, we argue that it is imbued with more features and applies to a broader set of examples than prior treatments. To demonstrate this, we examine its common relevance to two otherwise disparate modern epidemics: cholera and hepatitis C virus. The study proceeds in stages: (1) we first introduce a purely theoretical iteration of WAIT using a standard epidemiological model, explaining how to conceptualize a given infection in terms of indirect transmission, and deriving the reproductive number (R_0) using analytical methods. (2) We apply the WAIT perspective to a waterborne disease

that has been the object of several modeling exercises: the transmission of *Vibrio cholerae* in a densely populated setting with limited access to clean drinking water. (3) We then apply the WAIT perspective to a completely different, less-explored disease case: an HCV epidemic among injection drug users (IDU) in a modern urban setting. These constitute different epidemics in terms of pathogen type (*Vibrio cholerae* is a Gram-negative bacterium, HCV a single-stranded RNA virus) and setting. Nonetheless, we conceptualize and model each epidemic scenario, highlighting mathematical features that are unique to the WAIT framework. We discuss how this lens provides new perspective on cholera outbreaks and especially the modern HCV epidemic.

II. INITIALIZING WAIT: AN ELEMENTARY ADAPTED S-I-R ITERATION

A. Description

While the emphasis of our examination will reside in how we analyze several modern epidemic systems with the WAIT framework, for explanatory purposes we will begin by describing how it modifies very basic concepts in a classic, purposefully prosaic susceptible-infected-recovered (S-I-R or SIR) mathematical model. While this is analogous to prior methods used to discuss indirect or environmental transmission [17], a full appreciation of both cases discussed in this study (cholera and HCV) would benefit from a full, transparent explanation of the WAIT model-building process. The method is defined by modeling changes in a population of susceptible hosts ("S"), infected hosts ("I") and recovered ("R"). Classically, flow through the system is defined by contact between susceptible and infected individuals, often driven by a β factor, or transmission coefficient.

The WAIT framework would apply to a scenario where the individuals in such a system become infected through an environmental intermediate. Figure 1 is a compartmental model that depicts this interaction, with the two [W] (for "WAIT") compartments influencing (dashed line) the flow of hosts from the susceptible to infected compartments.

B. The adapted SIR compartmental diagram

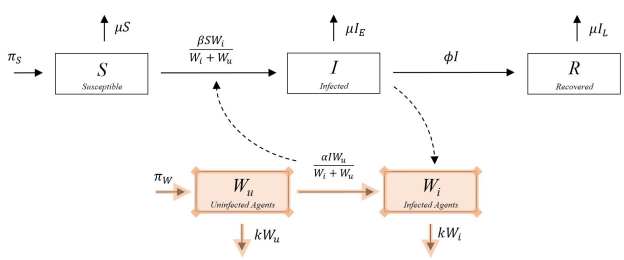

Fig. 1: ***Adapted SIR* compartmental diagram.** This depicts a standard SIR style compartmental model with the added compartments (shaded) corresponding to the WAIT environment. Note the dynamical properties of the W_i and W_u compartments. It is these dynamics that set the WAIT perspective apart from others: environments are often dynamical systems, with an ecology of their own.

The S, I, and R compartments represent the usual *susceptible*, *infected*, and *recovered* populations of hosts. W_u and W_i represent uninfected and infected populations of *environmental* hosts, respectively.

In traditional SIR models, the rate of new infection (arrow from the S compartment to the I) is generally proportional to the product of the susceptible and the infected populations, i.e. proportional to SI. In the WAIT framework, the environmental compartment, and not a host, drives the rate of infection. In this specific example, the W_i compartment drives the infection such that the rate of infection is proportional to SW_i. The epidemic is then driven by a series of interactions: interactions between uninfected (susceptible) hosts S and the infected (transmitting) environmental compartment W_i and interactions between infected individuals I and the uninfected environmental compartment W_u. The epidemic is sustained through infected hosts I depositing pathogen into the environmental intermediate, creating new infection in the reservoir, which can then interact with and infect more susceptible hosts S, in a process resembling a feedback loop. The dynamics of such a system as we have chosen to model them are captured by the set of dynamical equations below and can be visualized in Figure 1. A derivation of the terms in the model can be read in the Supplemental Appendix.

$$\frac{dS}{dt} = \pi_S - \beta \frac{SW_i}{W_u + W_i} - \mu S \tag{1}$$

$$\frac{dI}{dt} = \beta \frac{SW_i}{W_u + W_i} - \nu I - \mu I \tag{2}$$

$$\frac{dR}{dt} = \nu I - \mu R \tag{3}$$

$$\frac{dW_u}{dt} = \pi_W - \alpha \frac{IW_u}{W_u + W_i} - kW_i \tag{4}$$

$$\frac{dW_i}{dt} = \alpha \frac{IW_u}{W_u + W_i} - kW_i \tag{5}$$

C. Analytic Equations

Equations 1–5 define the prosaic SIR model. π_S is the birthrate of new susceptible hosts in the environment and μ is the fractional death rate of hosts. In this context, β represents the *strength* of the interaction between the susceptible hosts S and the environment. This will generally be proportional to the rate of contact between the two. Similarly, α characterizes the strength of interaction between infected hosts I and the environmental reservoir and is also generally proportional to the contact rate between the two. ν represents the fractional recovery rate, π_W is the birthrate of new uninfected environmental agents, and k is the fractional death rate of the environmental hosts.

D. WAIT framework influences the basic reproductive number in a standard SIR model

As an example of how the WAIT model provides a new take on traditional concepts, we briefly consider how the value of the basic reproductive ratio R_0 in this model

compares to its SIR counterpart. While R_0 can have different theoretical formulations, we rely on definitions as provided by Jones (2007) [32] and Diekmann et al. 2009 [33]. In a traditional SIR model the R_0 value is given by:

$$R_0^{SIR} = \frac{\beta \pi_S}{\nu \mu} \tag{6}$$

or sometimes, more simply, $R_0^{SIR} = \beta/\nu$, if one sets $\pi_S = \mu$ (birthrate cancels the death rate). β in this equation is the traditional transmission coefficient. In this classic case, it represents the coupling strength between two non-environmental agents, not between the environment and the traditional hosts, as in the WAIT. π_S, μ, and ν have the same interpretation as in our model.

Alternatively, the value of R_0 for the WAIT iteration takes the form:

$$R_0^{WAIT} = \sqrt{\frac{\alpha \beta \pi_S}{\nu \mu \pi_W}}. \tag{7}$$

In the WAIT iteration, β still represents a transmission coefficient, but between the environmental intermediate and the susceptible hosts S. α is the transmission coefficient between the environment and infected hosts I.

The R_0 formulae (equations 6–7) highlight differences between the models: The square root arises as a consequence of implementing two infected agents (I and W_i) into the model, as opposed to just one in the SIR case. Next, one notices that the β factor in the SIR formula is augmented by the additional factor α in the WAIT formula, representing a kind of shared dependence between the couplings controlling the I interaction (α) and the S interaction (β) with the environment. Analogously, what was the responsibility of π_S in the SIR formula is now a shared dependence on π_S/π_W, the ratio of the birthrate of susceptible hosts to that of uninfected environmental agents. In this case, the two appear as a ratio under the square root, as opposed to a product in the $\alpha\beta$ case, indicating that these parameters have opposite effects on the value of R_0: when π_W is increased R_0 decreases but when π_S is increased R_0 increases. Whereas, both the α and β terms will increase the value of R_0 when increased. This presentation allows one to disaggregate the dependencies of the disease burden, as parameterized by R_0, between *hosts* and *environmental agents*.

We observe that the R_0 can be written in a way that highlights more explicitly how the environmental reservoir shares dependence with the host parameters. The endemic equilibrium value for S is given by $S^* = \pi_S/\mu$ and the equilibrium value for W—the sum of the infected and uninfected portions of the reservoir, i.e. $W = W_i + W_u$—is given by $W^* = \pi_W/k$. This allows one to write the following equation:

$$R_0^{WAIT} = \sqrt{\frac{\alpha\beta}{\nu k}\frac{S^*}{W^*}}. \tag{8}$$

Writing R_0 in this way reveals the dependence of R_0 on the death rate k of the W compartments. From this perspective, it can be seen that ν and k (recovery rate of hosts and death/loss rate of environmental agents) share their role in R_0 in much the same way that β and α do in the numerator, and that S^* and W^* do as a ratio. This more symmetric form of R_0 highlights the importance of introducing the environment into the model. In doing so, one can see how the disease burden is modified in the presence of an interacting dynamical environment (viz., one can compare with $R_0^{SIR} = \beta S^*/\nu$, with $S^* = \pi_S/\mu$, which is an analogous way of writing eq. 6). By stressing the role of environmental reservoirs, this modelling perspective has the capacity to dissect properties of dynamics that other models may omit.

E. Basic rules for building a WAIT model

Constructing models using the WAIT framework requires an understanding of the specific biologies of the agents involved in the system of interest. Consequently, the use of the WAIT framework is as much a conceptual exercise as it is a mathematical one, driven by domain expertise on the problem of interest. The implementation of the framework can be summarized by three key concept-activities:

- Identify the relevant agent-compartments that define the dynamics of the system of interest (e.g. S, I, R, latent infected, etc.) and construct a compartmental model that captures interactions between them.
- If infection in the system is driven by interactions between hosts and an environmental reservoir, one can consider and model dynamics of the latter independently. One should ask how pathogens are deposited in this reservoir, and if/how the pathogen of interest replicates and/or survives in this setting. This is a key point of innovation, as it allows the modeler to think carefully about the biology and ecology of the environmental reservoir.
- Consider how the WAIT reservoir interacts with hosts. How does this interaction occur? What parameters would define how effectively pathogens are transmitted into the reservoir? Note that the nature of this reservoir can be diverse: it can be large or small, liquid or solid, mobile or immobile, and there could also be multiple reservoirs.

Having proposed a brief outline for how to think about and model a disease system using the WAIT perspective, we will apply it to two different, modern epidemic scenarios: first cholera in a densely populated setting with limited access to clean drinking water, and then hepatitis C virus in a community of injection drug users.

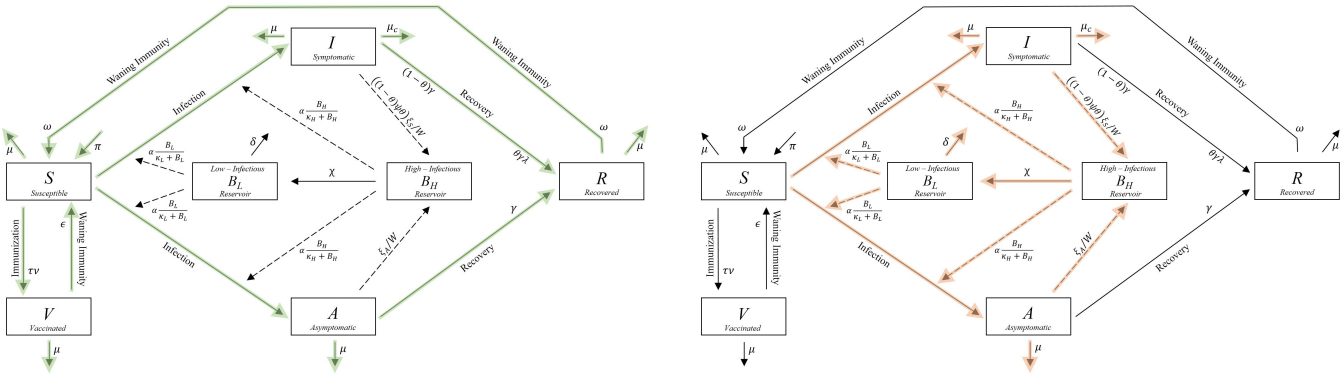

Fig. 2: **Cholera compartmental diagram**. **Left**: Green arrows highlight the flow of the population of hosts through the system. **Right**: here the red arrows highlight flow of disease through the system

III. THE CHOLERA WAIT MODEL

A. Description

Here we present a WAIT-style model of cholera (caused by the gram negative bacterium *Vibrio cholerae*), which has been the object of prior modeling efforts [12], [27]–[29], [31]. This specific iteration is based on a simulation of a 2010 outbreak in Haiti [30]. It is set with a population of 400,000 (the approximate population of the Carrefour section of Port Au Prince, Haiti), features seven ordinary differential equations, seven compartmentalized agents, and twenty parameters. It contains high-infectious and low-infectious water reservoirs, which are the mode of transmission [34]. Recent studies have examined other modes of transmission in cholera, (including transmission within households) [35], but we have chosen to focus on waterborne transmission. Treatment and prevention is undertaken via vaccination, antibiotic administration, and modification of the contaminated water dynamics.

B. Cholera WAIT model: compartmental diagram

The model can be visualized using a compartmental diagram as seen in Figure 2. Some general features, which reflect findings in prior studies [30], [34], [36], include the following:

- Disease is acquired by individuals as they become infected from drinking water from either the low-infectious or high-infectious reservoirs.
- Infected individuals (symptomatic and asymptomatic) shed bacteria into the high-infectious reservoir.
- Bacteria are removed from the system either via decay in the low-infectious reservoir, or via the death of infected individuals. These reservoirs differ in how much *V. cholerae* exist in a given amount of water, with the high-infectious reservoir much more likely to cause disease.
- Some individuals are vaccinated and individuals return to the susceptible compartment as their vaccine induced immunity wanes.
- Individuals enter and exit the system via equal natural birth and death rates, as well as a death rate due to the disease. Since natural birth and death rates are equal, and additional death can occur from disease, there is a loss of susceptible individuals as the model moves forward through time.

C. Cholera WAIT model: Analytic equations and parameters

The set of ordinary differential equations (Eq. 9–15) define the dynamics of the system. As outlined in the "elementary adapted S.I.R example," the environmental dynamics are realized within their own set of differential equations.

$$\frac{dS}{dt} = \mu N + \omega R + \epsilon V - \alpha S \frac{B_L}{\kappa_L + B_L} - \alpha S \frac{B_H}{\kappa_H + B_H} - \mu S - \tau\nu \tag{9}$$

$$\frac{dI}{dt} = (1-p)\alpha S \frac{B_L}{\kappa_L + B_L} + (1-p)\alpha S \frac{B_H}{\kappa_H + B_H} - (\mu_c + \mu + (1-\theta)\gamma + \theta\gamma\lambda) I \tag{10}$$

$$\frac{dA}{dt} = p\alpha S \frac{B_L}{\kappa_L + B_L} + p\alpha S \frac{B_H}{\kappa_H + B_H} - (\mu + \gamma) A \tag{11}$$

$$\frac{dR}{dt} = ((1-\theta)\gamma + \theta\gamma\lambda) I + \gamma A - (\mu + \omega) R \tag{12}$$

$$\frac{dV}{dt} = \tau\nu - \epsilon V - \mu V \tag{13}$$

$$\frac{dB_H}{dt} = (\psi\theta + (1-\theta)) \frac{\xi_s}{W} I + \frac{\xi_A}{W} A - \chi B_H \tag{14}$$

$$\frac{dB_L}{dt} = \chi B_H - \delta B_L \tag{15}$$

Table I lists the parameters and values used in this simulation. Of note, the $\frac{B_{L,H}}{\kappa_{L,H} + B_{L,H}}$ terms in Eq. 9–11 quantify the likelihood that an individual, per day, will be infected with *V. cholerae* given the contaminated water consumption rate α. These terms are constructed using the low and high infectious reservoir dose in units of cells per day. Other notable terms include, ν the vaccination rate, α the

contaminated water consumption rate, ξ_s the symptomatic individuals excretion rate, λ the relative recovery rate of those receiving antibiotics, and θ the proportion of individuals that are symptomatic and receiving antibiotics.

The initial conditions across all simulations included a population of 400,000 susceptible individuals with an initial small amount of *Vibrio cholerae* present in each reservoir to prime the outbreak (5 liters of the total water supply). Additionally, the values of the symptomatic, asymptomatic, vaccinated, and recovered compartments were set to zero.

D. Cholera WAIT model: disease dynamics

The simulation was constructed with a time step resolution of 10,000 over a period of 130 days. Figure 3 provides an overview of the dynamics of the disease and the effect of potential interventions. From these simulations, we can observe the behavior of the infected populations (symptomatic and asymptomatic), both of which grow rapidly in the first 20 days of simulation time (Figure 3A). The symptomatic group peaks first, shortly after which the asymptomatic group rises to a higher value. The decay that is seen in the latter days of the outbreak naturally occurs as the total number of susceptible individuals decreases. Further discussion regarding the long term behavior of the model, as well as the susceptible, recovered and vaccinated populations can be found in the Supplemental Appendix.

Using the WAIT environmental reservoir equations, one can model the relative changes in water reservoir infectiousness. In Figure 3b, we observe the high-infectious reservoir peak first, driven by the symptomatic population's shedding of bacteria into the aquatic environmental reservior. This behavior is is propelled by high excretion rate of symptomatically infected individuals (ξ_s), which is three orders of magnitude larger than (ξ_A). The high-infectious reservoir drives the rise of new infected cases. As the system moves forward in time, the high-infectious reservoir decays via the χ parameter, which shifts the disease-driving burden to the low-infectious reservoir.

Vaccination is approximated as a constant number of individuals vaccinated per day, resulting in a linear increase in the vaccinated population. On long time scales (greater than 2500 days) the recovered population peaks and declines as the total number of susceptible individuals ultimately decays, which no longer resembles realistic disease dynamics. Further exploration of this behavior can be found in the Supplemental Appendix.

E. Cholera WAIT model parameters influence the R_0

The R_0 provides a signature of the average infectiousness of a given pathogen in a given setting [32], [33]. In this model, given the parameters, $\mathbf{R_0 = 0.199}$ (A derivation of the analytic expression for R_0, as well as details regarding the sensitivity analysis, can be found in the Supplementary Appendix.) Thus, in its current configuration, the model does not describe a self-sustaining epidemic. (This is observable through the decay of the asymptomatic and symptomatic cases as depicted in Figure 3a). Additionally, the eigenvalues of the Jacobian matrix for the ODE system at the disease-free equilibrium are real numbers less then or equal to zero, with the largest eigenvalue being zero. Consequently, given enough time, the flow of disease will move to the diseaes free equilibrium.

Label	Value	Units	Definition	Sources
α	0.003	*(person day)*$^{-1}$	Rate of contaminated water consumption	[37]
κ_L	10^5	*cells / day*	Low-infectious *V.cholerae* Infectious dose	[38]
κ_H	2000	*cells / day*	High-infectious *V.cholerae* Infectious dose	[39]
χ	1	*% / day*	Rate of decay from high-infectious to low-infectious water	[40]
δ	$0.\overline{33}$	*% / day*	Environmental death rate of *V. cholerae*	[?]
μ	$4.49 \cdot 10^{-5}$	*% / day*	Natural birth & death rate	[41]
μ_c	0.046	*# / day*	Symptomatic mortality rate	[42]
γ	0.20	*% / day*	Disease recovery rate	[43]
p	0.79	*% / day*	Proportion of asymptomatic cases	[44]
ξ_S	$1.30 \cdot 10^{11}$	*cells / day*	Symptomatic excretion rate	[45]
ξ_A	$1.30 \cdot 10^{8}$	*cells / day*	Asymptomatic excretion rate	[46]
ω	$3.42 \cdot 10^{-3}$	*% / day*	Waning of natural immunity	[47]
ν	1000	*vaccines / day*	Vaccination rate	[48]
τ	0.67	*% / day*	Vaccine efficacy	[49]
ϵ	$1.37 \cdot 10^{-3}$	*% / day*	Waning vaccine induced immunity	[50]
θ	0.08	*% / day*	Proportion symptomatic & receiving antibiotics	[51]
ϕ	0.52	*% / day*	Rate at which persons receiving antibiotics shed bacteria into reservoir	[52]
λ	2.30	*% / day*	Relative recovery rate receiving antibiotics	[43]
W	$1.5 \cdot N$	*Deciliters*	Size of water reservoir	[53]
N	$4 \cdot 10^5$	*People*	Number of individuals	—

TABLE I: Cholera WAIT model parameters

The relative sensitivity of R_0 to changes in the model parameters was examined, and we find that p, W, α, and χ_S are the four most sensitive parameters. These include two parameters strongly related to WAIT aspects of the model: the rate of contaminated water consumption α, and the total water reservoir size W. Further analysis was also conducted to better understand how adjustments to the model parameters can push $R_0 > 1$. The results of these analysis can be found in the Supplemental Appendix.

F. Cholera WAIT model and simulated interventions: antibiotics, vaccination and water purification

Having explained the model structure and analyzed parameter influences on the basic reproductive ratio, we then

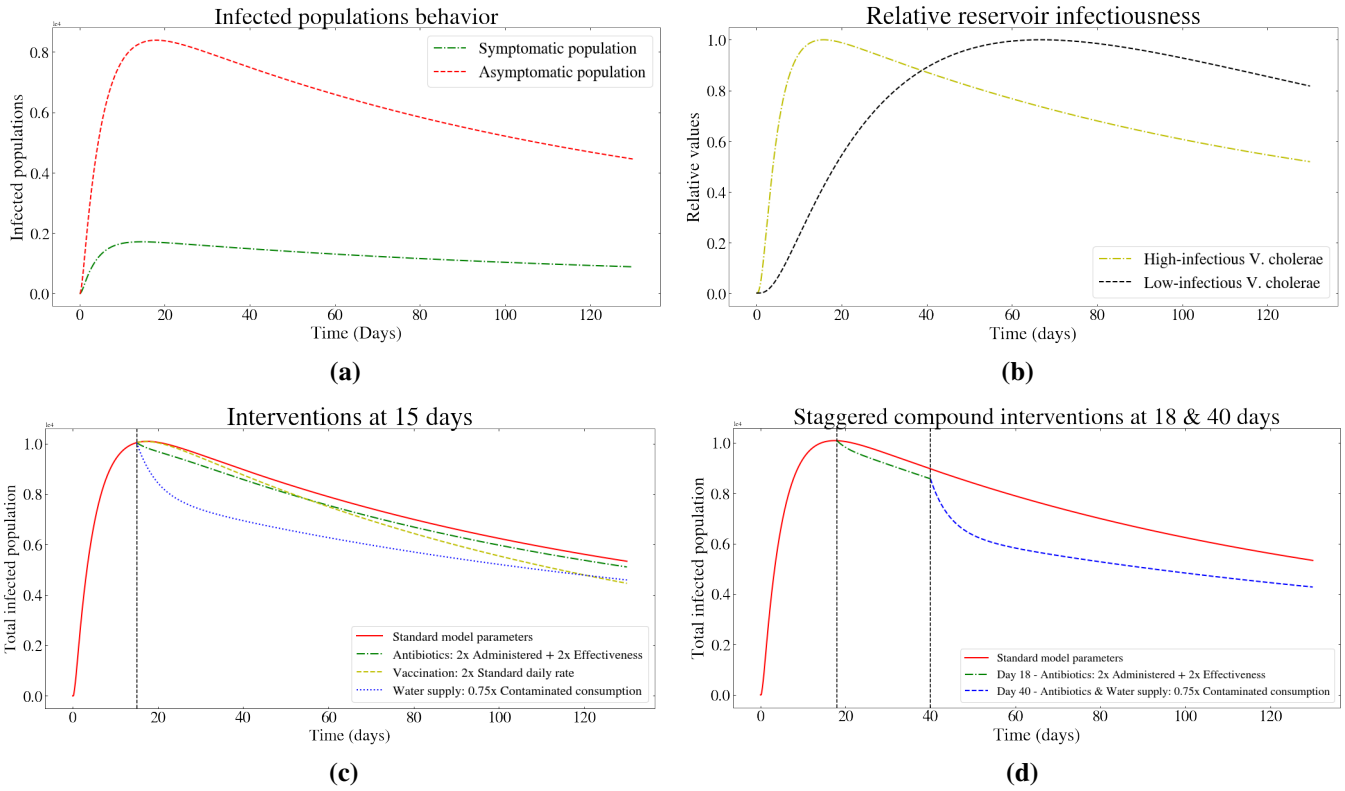

Fig. 3: **Cholera WAIT model dynamics and simulated interventions**. **(a)**: The dynamics of both the symptomatic and asymptomatic infected populations. **(b)**: The fractional relative infectiousness of each reservoir (normalized to 1). **(c)**: Antibiotic, vaccine, and water purification interventions applied at 15 days after the start of the model outbreak **(d)**: Compound staggered interventions mimicking an example real world disease management strategy

analyzed a range of potential interventions, comparing their impact on various properties of the cholera dynamics. Specifically, we examine three types of interventions: vaccination, antibiotic administration, and water purification. Each were realized by modifying the respective model parameters that encode information relevant to that intervention.

Figure 3 shows various iterations of the simulation, tracking the sum of both symptomatic and asymptomatic individuals in the standard model (Figure 3a), with various different interventions implemented (3c, 3d). In Figure 3c, we observe how the the effect of daily vaccine administration manifests most clearly in the longer term (>100 days) behavior of the dynamics, where it can eventually exceed the effects of reduction in contaminated water consumption (if vaccine effectiveness is sufficiently high). We can also see the large impact of instantaneously reducing contaminated water consumption on the number of infected individuals (in terms of both number of infected individuals, and the rate at which that impact manifests). For example, increasing antibiotic, and vaccine administration two-fold has less immediate impact on disease dynamics than decreasing contaminated water consumption even by a quarter. Together, the cholera WAIT model offers the hypothesis that ideal interventions might include a combination of long-term (e.g. vaccination) and short-term (e.g. water purification) interventions to limit the number of infected cases.

Lastly, compound intervention dynamics are considered (Figure 3d). These aim to simulate disease management strategies where, given practical strategies such as resource allocation and response time, a staggered or combined response is more likely to be implemented. We chose this particular compound intervention to demonstrate how the WAIT model can broadly accommodate the types of modifications that represent public health interventions.

IV. THE HEPATITIS C VIRUS WAIT MODEL

A. Description

The HCV model describes a population of approximately 170,000 individuals—based on estimates of the size of the IDU community in New York City [54]—where infected injection drug users may migrate into the population. In this model, needles serve as the environmental intermediate for infection, and the sharing of infected needles will constitute the means of transmitting new infection. Note that while the term "needle" is only one part of a syringe, we use it to refer to the entire syringe. HCV can also be transmitted sexually [55], but in this paper we restrict our attention to transmission through infected needles. As with the cholera model, this section of the main text focuses on the main structure and dynamical properties of the model. Further model details and discussion can be found in the Supplemental Appendix.

B. HCV WAIT model: Compartmental diagram

We model the dynamics of needle populations, injection drug users, and infected individuals through a series of five ordinary differential equations. The compartments, labeled S, I_E, I_L, N_u, and N_i represent the populations of susceptible individuals, early-infected individuals (sometimes referred to as acutely infected), late-stage infected individuals (sometimes referred to as chronically infected), uninfected needles, and infected needles, respectively. This model has several features:

- The susceptible compartment refers to individuals who are injecting drugs and who are sharing needles with other members in the IDU community.
- The needle population is divided into two compartments: infected and uninfected, and we model the dynamics of each compartment separately.
- New infections (of both people and needles) will depend on the fraction of infected or uninfected needles in circulation.
- There are various estimates for the ability of HCV to survive in needles [56] [57]. We incorporate HCV free-living survival via the parameter ϵ, which quantifies the rate at which the virus spontaneously clears from infected needles.

C. HCV WAIT model: Analytic equations and parameters

The dynamics of the HCV transmission process are governed by equations 16–20. The population of individuals who are being treated and those who have recovered are not explicitly modeled in this WAIT iteration, as the dynamics of treatment and recovery are not central to the questions explored in this study. There are, however, several modeling studies of HCV that focus on treatment [58]–[61], and their effects are not ignored in the HCV WAIT model. Entering or leaving treatment (and re-entering the susceptible population, as in case of drug relapse in the IDU population) are approximated by the "birth" terms π_S and π_T and removal terms $-\tau I_L$ and $-\tau I_E$.

$$\frac{dS}{dt} = \pi_S + \phi(I_E + I_L) - c\beta S\frac{N_i}{N_i + N_u} - \mu S \tag{16}$$

$$\frac{dI_E}{dt} = \pi_I + c\beta S\frac{N_i}{N_i + N_u} - (\omega + \tau + \mu + \phi)I_E \tag{17}$$

$$\frac{dI_L}{dt} = \pi_T + \omega I_E - (\mu + \tau + \phi)I_L \tag{18}$$

$$\frac{dN_u}{dt} = \pi_N - k_u N_u - \gamma\zeta(I_E + I_L)\frac{N_u}{N_i + N_u} + \epsilon N_i \tag{19}$$

$$\frac{dN_i}{dt} = \gamma\zeta(I_E + I_L)\frac{N_u}{N_i + N_u} - k_i N_i - \epsilon N_i \tag{20}$$

π_S is the birthrate (via migration or first-time use) of new members into a given community of injection drug users (constant in this model). This includes those who may be returning to the population of IDU after recovering from HCV. π_T represents the rate of individuals entering the infected stage coming from an unsuccessful treatment program. ϕ represents the daily fraction of individuals infected with HCV who spontaneously clear the infection. c represents the rate of sharing a needle with another user (infected or otherwise) per capita. β represents the probability that an uninfected individual will convert to HCV+ after injection

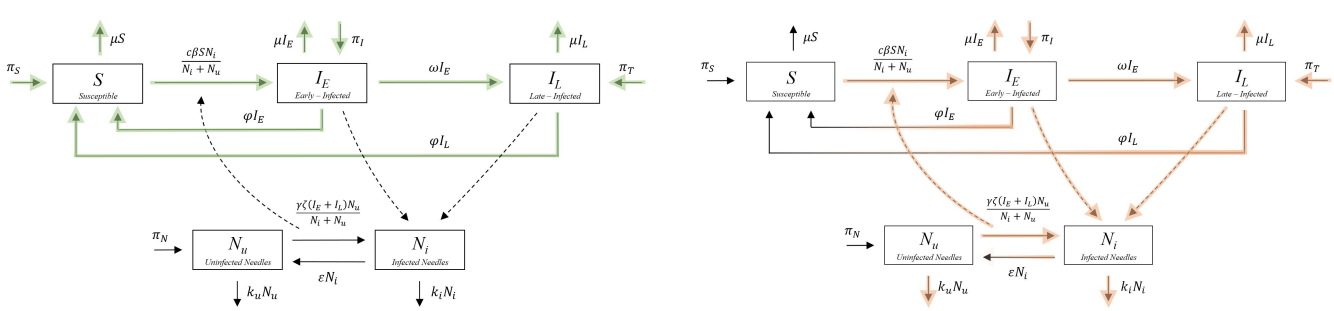

Fig. 4: **Hepatitis C virus compartmental diagram. Left**: Green arrows highlight the flow of the population of hosts through the system. **Right**: Red arrows highlight flow of disease through the system, and where there is a color/transparency gradient there is a flow of infection away from an infected compartment towards an uninfected one.

with an infected needle. μ is the combined fractional death and IDU cessation rate (individuals who leave the IDU community). π_I represents the rate of migration of early stage infected individuals into the study population of IDU (assumed to be constant). ω is the daily fraction of early-stage infected individuals who progress to the the late-stage of infection. τ is the daily fraction of infected individuals who go into treatment. π_N is the rate of introduction of uninfected needles into the population of IDU. γ is the average number of injections per user per day. ζ represents the probability that a new needle becomes infected after use by an infected user. k_u is the daily fraction of uninfected needles which are discarded. k_i is the daily fraction of infected needles which are discarded. Lastly, ϵ is the fraction of infected needles which become uninfected in the period of a day due to de-activation (or "death") of virus populations on the needle. Parameter values and sources can be seen in Table II.

D. HCV WAIT model parameters influence the R_0

Having constructed and elaborated on the details of the HCV WAIT model, we now explore how parameters related to the environment (in this case, those framing the population of infected needles) influence the R_0. We directly measured the influence of parameters on the R_0 by considering the effect of modifying the parameters. The value of R_0 was calculated using established methods [32], [33] and is outlined in the Supplemental Appendix.

$$R_0 = \sqrt{\frac{c\gamma\zeta\beta k_u \pi_S}{\pi_N \mu(\mu+\tau+\phi)(\epsilon+k_i)}} \tag{21}$$

From the form of R_0 given in equation 21, one could surmise that several parameters in the formula have comparable sensitivities. We tested this directly by calculating the PRCC (Partial Rank Correlation Coefficient) for each of the parameters in the model, with respect to R_0, based on methods used in prior studies [62]. We find that parameters related to an interaction with the environmental reservoir (the population of needles) such as k_u (the fractional discard rate of uninfected needles), γ (the rate of daily injections per capita), and π_N (the birthrate of new needles) are as central to HCV dynamics as traditionally considered parameters, such as π_S (the birthrate of susceptibles), c (the contact or sharing rate of IDU), or μ (the combined death and cessation rate of IDU) (Figure 5). This fortifies the notion that WAIT-specific properties dictate the spread of HCV, providing opportunities to explore more precise targeting by public health interventions.

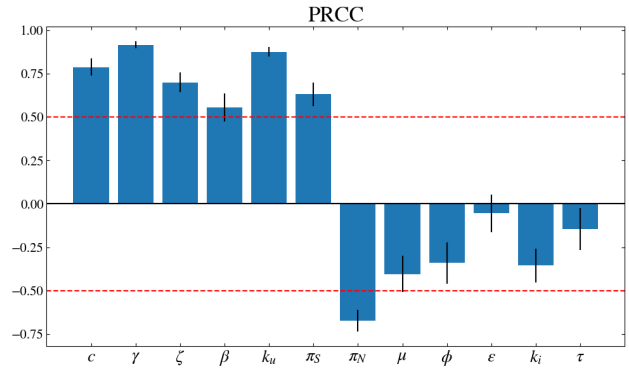

Fig. 5: **$\mathbf{R_0}$ sensitivity in HCV: the Partial Rank Correlation Coefficient (PRCC)**. A PRCC calculation was performed for R_0 using Latin Hypercube Sampling. Parameters were sampled from uniform distributions with widths specified by the ranges given in Table II. The PRCC calculation was repeated for 50 independent iterations. The average of these iterations is shown here, with the standard deviations for each parameter shown as the error bars.

E. HCV WAIT model and simulated interventions: needle-exchange programs

Having demonstrated the structural relevance of the WAIT framework in terms of how it influences the basic reproductive number, we can consider the utility of the model with respect to other properties, including how it offers insight into potential interventions.

One such intervention may be the implementation of needle-exchange programs. Needle-exchange programs are an example of "harm reduction" public health strategies that aim to reduce harm stemming from behaviors that put the affected individuals or communities at risk [63]. These policies are controversial, but have been demonstrated to be effective interventions for HIV and HCV in certain settings [64]. With respect to the HCV WAIT model, some of these programs (especially ones targeting injection equipment, like safe injection sites) can increase the discard rate of infected needles by providing a safe location to use and discard needles, while also providing uninfected needles to IDU. In our model, parameters like the needle discard rate, k_i and k_u, and π_N are affected by needle exchange programs. Figure 6 demonstrates how R_0 is affected by these parameters. One can see that R_0 can be reduced by increasing k_i—the infected needle discard rate—along a fixed value of π_N—the birthrate of uninfected needles—and that increasing π_N along a fixed value of k_i has the same effect. It is also evident that R_0 can be reduced more rapidly by increasing k_i and π_N simultaneously, as expected. In this way, the proportion of infected needles is reduced because of an increase in clean needles and a reduction of infected ones, lowering R_0.

In Figure 6, we demonstrate how changing k_u and k_i modifies the value of R_0. Notice that R_0 is reduced by increasing k_i across fixed values of k_u. The opposite effect is observed when increasing k_u along fixed values of k_i. That is, removing infected needles at an increased rate may

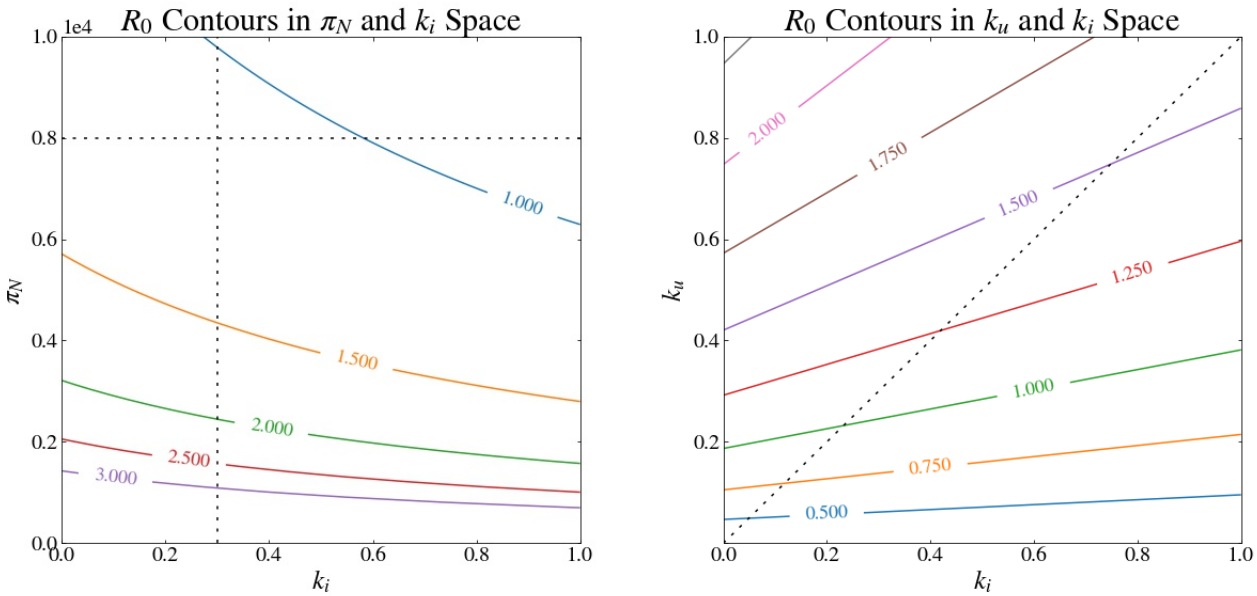

Fig. 6: **HCV $\mathbf{R_0}$ as a function of various model features**. **Left**: The relationship between the rate of acquisition of clean needles π_N and the discard rate of infected needles k_i with respect to various values of R_0. The curves are contours of constant values of R_0 and are labelled as such. The vertical and horizontal dashed lines indicate the chosen values for their respective parameters. **Right**: The relationship between the infected and uninfected needle discard rate, with respect to R_0. The diagonal line represents when $k_u = k_i$. Notice that moving upwards along this diagonal increases R_0.

Label	Value	Units	Definition	Sources
π_S	300 ± 100	*person / day*	Birthrate of susceptibles (entering the IDU community)	Estimate
π_T	25 ± 10	*person / day*	Rate of treatment failure	Estimate
ϕ	0.26 ± 0.05	*% / day*	HCV self-clearance fraction per day	[58] [65]
c	1 ± 0.5	*shares / day*	Daily sharing rate of needles per capita	[66]
β	0.018 ± 0.005	%	Probability of infection from an infected needle	[67]
μ	$(2.7 \pm 0.5) \cdot 10^{-4}$	*% / day*	Fractional rate of removal from IDU community due to cessation & death	[68]
π_I	40 ± 10	*person / day*	Migration rate of new early infected into IDU community	Estimate
ω	0.5 ± 0.3	*% / day*	Birthrate of late infections as a fraction of early infections	[69] [70]
τ	0.04 ± 0.02	*% / day*	Fractional rate of entering treatments	[71] [72]
π_N	$(8 \pm 3) \cdot 10^3$	*needles / day*	Birthrate of uninfected needles	[73] [74]
γ	2.5 ± 2	*injections / day*	Daily rate of injections per capita	[70] [74]
ζ	0.25 ± 0.1	%	Probability of transferring infection to a needle	[75]
k_u	0.3 ± 0.2	*% / day*	Fractional discard rate of uninfected needles	Estimate
k_i	0.3 ± 0.2	*% / day*	Fractional discard rate of infected needles	Estimate
ϵ	0.96 ± 0.03	*% / day*	Fractional decay rate of HCV infection in needles	[57]

TABLE II: HCV WAIT model parameters

decrease infection risk in a population of IDU, while doing the opposite can increase the risk. One can also see that increasing k_u and k_i simultaneously along the dashed line—where $k_u = k_i$—will increase R_0. This indicates that if a distinction between infected and uninfected needles cannot be established in a given setting, then it may be more helpful to add a higher proportion of uninfected needles than it would be to remove a higher proportion of all needles.

V. DISCUSSION

In this study, we propose a framework—the waterborne, abiotic and other indirectly transmitted pathogen paradigm (WAIT)—for modeling infectious diseases where transmission is dictated by an interaction between hosts and an environmental reservoir. We use it to explore two very different modern epidemics of significant public health consequence: cholera and hepatitis C virus. We first establish it through a simple form, an elementary adapted SIR formulation, and highlight how it modifies fundamental properties of epidemics such as the basic reproductive number (R_0). We then build mathematical models to explore cholera and HCV disease dynamics. We demonstrate how the integrated framework highlights potentially overlooked properties of these systems, and highlights potential avenues for intervention. The model is compatible with existing canon in epidemiology, and can accommodate theory in the ecology and evolution of infectious disease. For example, the "curse of the pharaoh hypothesis," which predicts that pathogens that with high free-living survival can be more virulent [76], can be modeled on a population scale using the WAIT

framework. In addition, questions regarding how changes in climate and environment may influence the spread of diseases can also be readily examined.

In the context of cholera, modeling the aquatic reservoir allows us to interrogate the interplay between several notable aspects of cholera epidemics. For example, the interaction between the relative size of the body of water and changes in infected populations, and the notion that the symptomatic and asymptomatic infectious populations fuel different aspects of the epidemic (initial and longer-term phase, respectively). These are areas of present and future inquiry.

In the context of HCV, the WAIT perspective reveals that the dynamics of injection needle populations are crucial to the spread of HCV, which offers a lens on approaches that might attenuate outbreaks of HCV. To the best of our knowledge, no existing mathematical model of HCV epidemiology has interrogated the dynamics in this manner. It is our hope that the HCV modeling community exploits and improves upon this perspective by further adapting the model to study HCV in specific settings.

More generally, The WAIT framework is driven by a contextual understanding of the disease dynamics, where the model parameterization follows the intuition of the scientist. Consequently, it broadens the scope of diseases that can be responsibly understood using mathematical or computational models, potentially generates hypotheses, and fosters improved recapitulation (and possibly prediction) of epidemics where indirect, environmental, transmission occurs.

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CODE AVAILABILITY

Code for the mathematical models presented in this manuscript are available on GitHub (https://github.com/OgPlexus).

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