Examining Control Strategies for Cholera Incorporating Spatial Dynamics

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April 6, 2019 @ 14:54

Abstract

Cholera has a significant impact on public health, especially in areas with poor water sanitation, with infections estimated to affect between 1.3 and 4 million people annually (WHO, 2019). Many people globally still lack proper infrastructure or access to clean water(Moe & Rheingans, 2006). While vaccines and antibiotics exist, vaccination can be difficult to achieve at necessary levels for stopping an epidemic and widespread antibiotic usage contributes to the development of antibiotic resistance. Considering the spatial dynamics of water sanitation, antibiotic usage and vaccination are important for creating the most effective and efficient treatment regime in preventing cholera epidemics

Contents

1 Introduction

1.1 Biology of Cholera

Although it is listed as one of the oldest known diseases, cholera remains a major public health concern in areas with poor water sanitation with an estimated 1.3–4 million cases every year (WHO, 2019). Cholera is an infectious disease caused by the bacterium *Vibrio cholerae*. The bacterium survives and reproduces in aquatic environments, and is capable of colonizing small intestines (Codeco, 2001). The disease is not airborne, but can be transmitted through contaminated food or water and can survive in some aquatic environments from months to years (Tien & Earn, 2010). The bacterium produces enterotoxins responsible for the symptoms of cholera infection which are severe diarrhea, vomiting and nausea (Kaper *et al.,* 1995). Dehydration thickens the blood, causing circulation problems that can lead to death within a few hours. Since dehydration is the main problem, rehydration with clean water and minerals (such as oral rehydration salts (ORS) packages) is the most effective treatment (WHO, 2019). Current improvements in public health and sanitation largely decrease the likelihood of a cholera outbreak (WHO, 2019).

Four major outbreaks of cholera in the 19th century devastated the London population, resulting in tens of thousands of deaths. One of the early theories believed to be the cause of spread of cholera was the Miasma theory, suggesting that cholera is an airborne disease and that impurities in the air induced the spread (Paneth *et al.,* 1998). Thus, the suggested solution in 1848 was to discard the contents of cesspools and raw sewage pits into the River Thames. Since Thames was the drinking source of many, the misunderstanding about the method of transmission resulted in heightened number of infected individuals, severely worsening the epidemic (Paneth *et al.,* 1998). Early studies on cholera, such as the work of John Snow in the mid 19th century, have been pivotal in the development of modern epidemiology. However, the abundance of more recent studies using mathematical models to anticipate outbreaks of cholera and planning for interventions is the reason for our focus on this particular disease.

1.2 Transmission Dynamics of Cholera

Before introducing a simple model to simulate the temporal spread of cholera, we must discuss the processes we plan to analyze. The model should include the entire population, which for simplicity we will assume is comprised of only three groups: the susceptible, the infected (or infectious), and the recovered. The only area still remaining that has a major impact on the epidemic is the environment, or in this case the water. We assume that only Infectious individuals can contaminate the water sources by shedding the pathogen into the water. The halting remedy suggested increased the rate of water contamination drastically, which in turn increased the transmission rate from individuals coming into contact with the infected water. This is a plausible explanation for why maximum weekly deaths in London increase more than two-fold in the 1848 epidemic compared to the 1832 epidemic (Tien, Poinar, *et al.,* 2011). The main treatment strategies for cholera outbreaks are vaccination, antibiotic treatment, and water sanitation. We can incorporate these into our model to simulate the effect that each of these strategies has on the disease dynamics.

1.3 SIRW Model Construction

Our model has four distinct departments: susceptible, infectious, recovered, and water compartments (Tien & Earn, 2010).

Susceptible The proportion of the population that is susceptible to being infected by cholera. Newborns are directly added to S at a rate μ. Individuals leave this compartment in one of two ways. They either die at a rate μ, or come into contact with the pathogen and move into the Infectious compartment. Our model assumes equal rates of natural birth and death. Interactions of susceptible and infectious individuals from the I compartment yields new infected individuals at a rate of β_I, and interactions of susceptible individuals with the water compartment W yields new infected individuals at a rate β_w.

Infectious The proportion of individuals that have been infected with cholera. Individuals in this compartment are capable of infecting susceptible individuals during interactions at a rate of β_i. They are also capable of contributing to the choleric load of the water compartment by shedding the pathogen at a rate ξ. Although for cholera the rate of transmission from person to person interactions is much lower in reality than the rate of transmission through contact with infected waters, we decided it still has enough significance to be in the model. Individuals in this compartment recover at a rate γ, and move to the recovered compartment, or they die naturally (not from Cholera) at a rate μ and from Cholera at a rate α. With advances in medicine over the past decades α is no longer a significant parameter in todays world.

Recovered The proportion of individuals that are neither infected with cholera nor susceptible to the pathogen. They leave this compartment as they die naturally at a rate μ.

Water The W term is proportional to the concentration of Cholera in the environment (or in this case the water). More bacteria enter the compartment as infected individuals shed the pathogen at a rate ξ, and the pathogen dies at a rate σ.

2 Single Patch Models

2.1 Model Introduction And Parameters

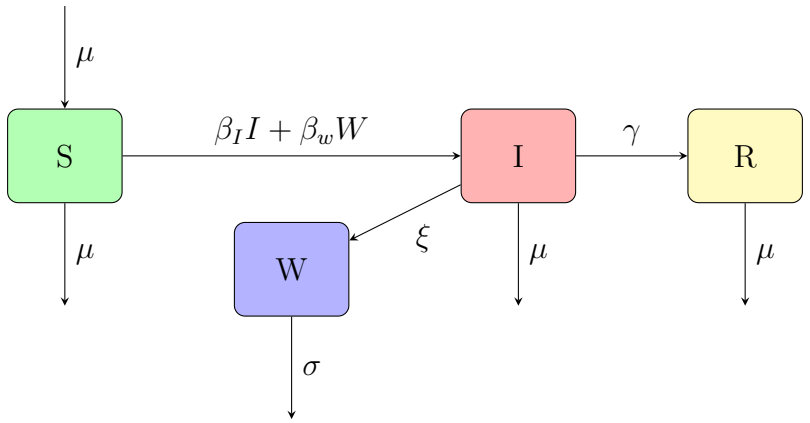
In this paper, we consider the cholera SIWR model as outlined by Tien and Earn Tien & Earn, 2010 with the addition of death rate by cholera σ. The tables below summarize the variables and parameters involved.

	Description	**Units**
S	Susceptible individuals	individuals
I	infected individuals	individuals
R	recovered individuals	individuals
W	Bacterial concentration in water	cells ml^{-3}
N	Total number of individuals	individuals

	Description	Units	Estimate
μ	Natural death/birth rate	day $^{-1}$	
b_i	Person-person transmission/contact rate	cells ml^{-3} day^{-1}	
b_w	water reservoir-person transmission/contact rate	cells ml^{-3} day^{-1}	
β_i	scaled Person-person transmission/contact rate	day^{-1}	0.25
β_w	scaled water reservoir-person transmission/contact rate	day^{-1}	1×10^{-5} to 1
$\frac{1}{\gamma}$	Infectious period	day	2.9 to 14
σ	Bacterial decay/removal from reservoir	day^{-1}	$\frac{1}{3}$ to $\frac{1}{41}$
ξ	Person to water reservoir shedding rate	cells ml^{-3} day^{-1} individuals^{-1}	0.01 to 10
α	Death rate by cholera	day^{-1}	0.01 to 0.6

Parameter estimates are taken from Grad *et al.*, 2012, Codeco, 2001 and Tien, Poinar, *et al.*, 2011. The natural death rate is dependent on various factors such as city or location and year or era of interest.

2.2 Single Patch SIR Model With A Water Compartment



$$\frac{dS}{dt} = \mu N - \mu S - \beta_I SI - \beta_w SW$$
$$\frac{dI}{dt} = \beta_I SI + \beta_w SW - I(\gamma + \mu + \alpha)$$
$$\frac{dR}{dt} = \gamma I - \mu R$$
$$\frac{dW}{dt} = \xi I - \sigma W$$

- μ = natural death rate
- β_I = transmission rate between S and I class

- β_w = transmission rate between I and W class
- γ = recovery rate (I to R class)
- α = death rate from cholera
- ξ = Shedding rate of cholera from I to W class
- σ = Removal rate of cholera from W class (depends on what we define as our water source)

The assumptions for this model are

- Individuals are assumed to be identical, and the population is homogenously mixed
- No waning immunity; once you recover from cholera you cannot return to the susceptible class
- The transmission rate between water the susceptible class is exponentially distributed

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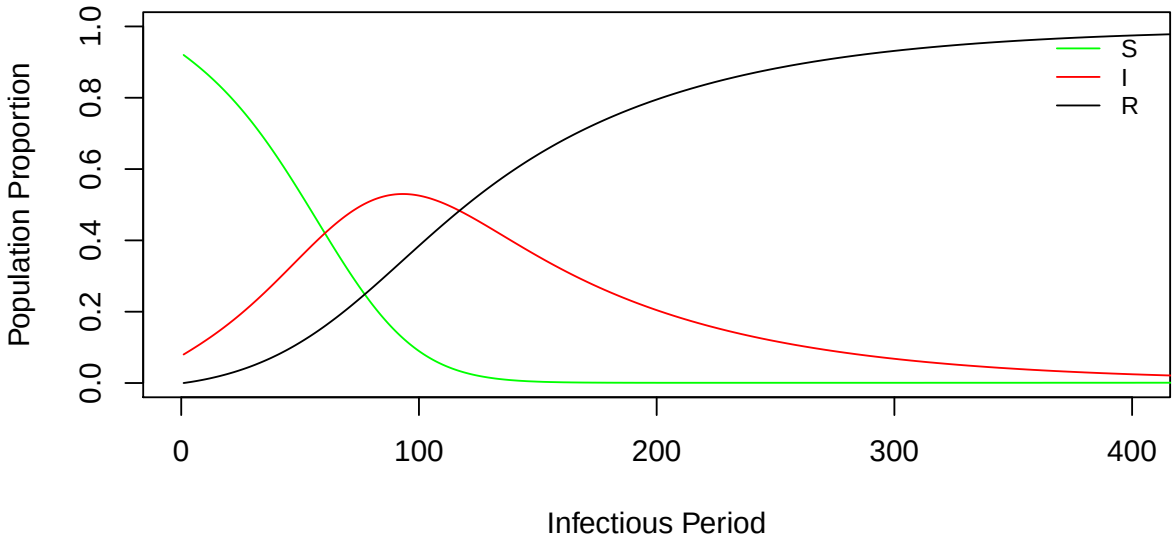

Figure 1: Plot of the SIRW model for a single patch. Parameters are $\mu = 0,\ \beta_I = 0.02,\ \gamma = 0.14,\ \sigma = 0.04,\ \beta_w = 0.5,\ \alpha = 0,\ \xi = 10$. Further the initial conditions for the model were $S_0 = 0.92,\ I_0 = 0.08,\ R_0 = 0$.

2.3 Equilibrium and $\mathcal{R}_0$ Of The Single Patch Model

The basic reproductive number $\mathcal{R}_0$ is defined as the expected number of secondary infections that result from introducing a single infected individual into an otherwise susceptible population. $\mathcal{R}_0$ can be computed as the spectral radius (i.e. the eigenvalue with the largest absolute value) of the next generation matrix at the disease free equilibrium. The next generation matrix FV^1, where entry F_{ij} of the matrix F is the rate at which infected individuals in compartment j produce new infections in compartment i, and the entry of V_{ij} of the matrix V is the mean time spent in compartment j after moving into j from compartment k. For our model, we have

$$F = \begin{pmatrix} \beta_i & \beta_w \\ 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} \frac{1}{\gamma+\mu+\alpha} & 0 \\ \frac{1}{\gamma+\mu+\alpha} & \frac{1}{\sigma} \end{pmatrix}$$

The basic reproductive number is computed as the spectral radius of FV^{-1} as seen in Tien & Earn, 2010, which is

$$\begin{aligned} \mathcal{R}_0 &= \rho(FV^{-1}) \\ &= \frac{\beta_i + \beta_w}{\gamma + \mu} \end{aligned}$$

This singla patch model has a stable disease-free equillibrium at (S,I,R)=(1,0,0) when $\mathcal{R}_0 < 1$. It also has a stable endemic-equillirbium when $\mathcal{R}_0 > 1$.

3 Multi Patch Model

The following equations represent the SIRW model for a single patch i in the multi patch model.

$$\begin{aligned} \frac{dS_i}{dt} &= \mu N - \mu S_i - \beta_i S_i I_i - \phi\beta_i S_i \sum_j^n I_j - \beta_w S_i W_i - \psi\beta_w S_i \sum_j^n W_j \\ \frac{dI_i}{dt} &= \beta_i S_i I_i + \beta_i \phi S_i \sum_j^n I_j + \beta_w S_i W_i + \beta_i \psi S_i \sum_j^n W_j - I_i(\gamma + \mu + \alpha) \\ \frac{dR_i}{dt} &= \gamma I_i - \mu R_i \\ \frac{dW_i}{dt} &= \xi I_i + \beta_i \psi I_i \sum_j^n W_j - \sigma W_i \end{aligned}$$

Where the set n in the set is all neighbours (i.e. adjacent and directly diagonal patches) of the patch i.

- μ = natural death rate

- ϕ = person to person contact rate between neighbouring patches
- ψ = person to water contact rate between neighbouring patches
- β_i = transmission rate between S and I class
- β_w = transmission rate between I and W class
- γ = recovery rate (I to R class)
- α = death rate from cholera
- ξ = Shedding rate of cholera from I to W class
- σ = Removal rate of cholera from W class (depends on what we define as our water source)

The assumptions for the single patch model apply here as well as the following.

- No dispersal of individuals between patches
- infected individuals in patch i can infect succeptible individuals in the neihgbouring patch j
- All patches neighbouring i have the same transmission rate to patch i

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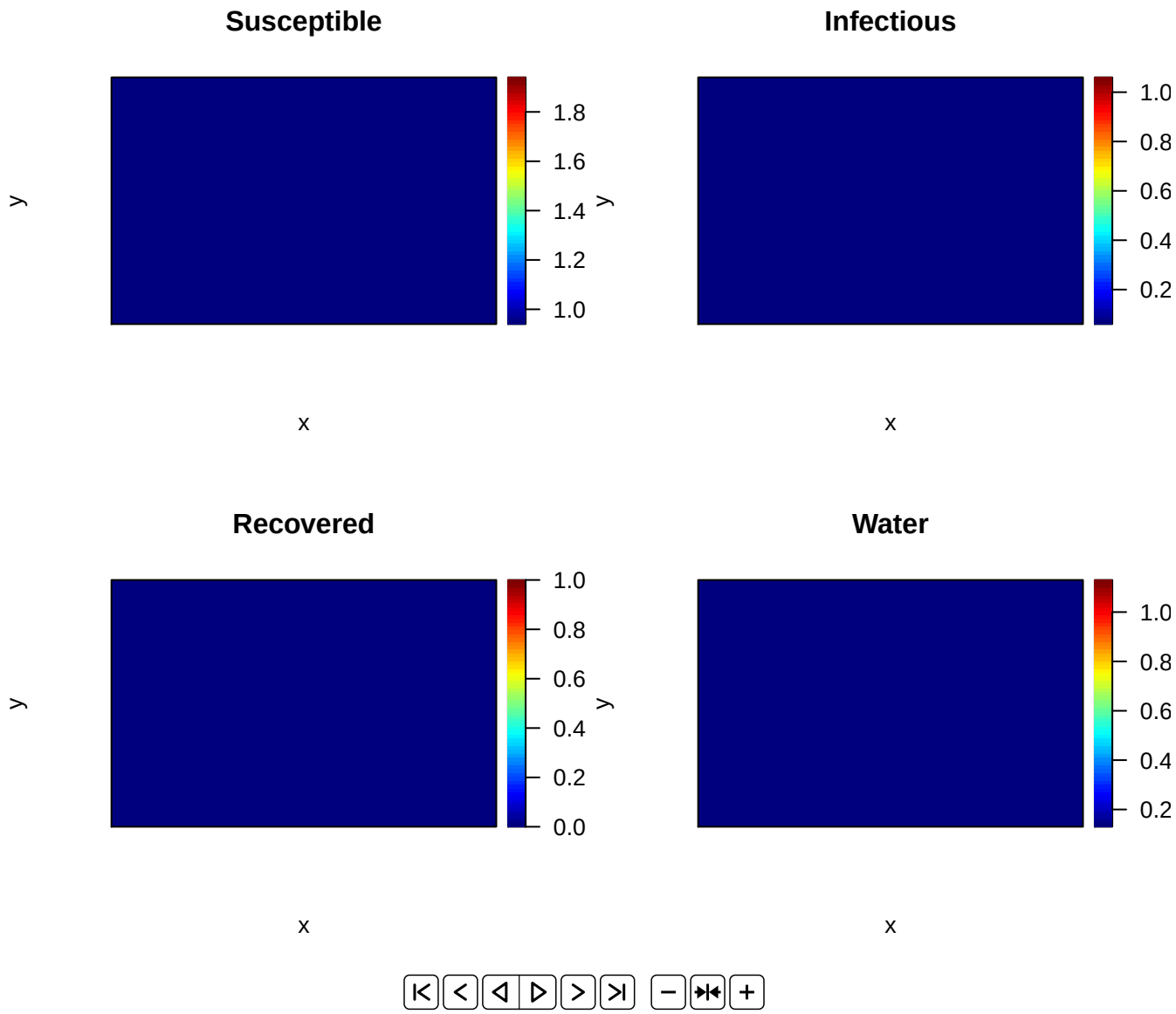

Figure 2: Plot of the SIRW model for all patches in a multi patch model. Parameters are $\mu = 0, \beta_i = 0.02, \gamma = 0.14, \sigma = 0.04, \beta_w = 0.5, \alpha = 0$ The initial conditions for the model were $S_0 = 0.94, I_0 = 0.06, R_0 = 0$,.

4 Treatment Strategies For Cholera

4.1 Treatment Plan 1: Sanitation of water over time

One of main ways control strategies for cholera is to treat the water directly (eg. with chlorine). This would essentially have the effect of increasing the rate of bacteria removal from water (defined as σ in the base single patch model). This can be modeled by incorporating a new term ρ in the base model:

$$\frac{dS}{dt} = \mu N - \mu S - b_i SI - b_w SW$$
$$\frac{dS}{dt} = b_i SI + b_w SW - I(\gamma + \mu + \alpha)$$
$$\frac{dR}{dt} = \gamma I - \mu R$$
$$\frac{dW}{dt} = \xi I - \sigma W - \rho W$$

This new term ρ can be either a constant which is implemented right at the start, or can be a function of time, or can be implemented at a certain threshold depending on the bacterial concentration (W) or the proportion of infecteds (I). For example:

$$\rho(I) = \begin{cases} \rho & I \geq 0.1 \\ 0 & 0 \leq I \leq 0.1 \end{cases}$$

This represents the sanitation rate of ρ, implemented at certain threshold of infected (in this case the threshold is based on $I = 0.1$ but can be based on W (i.e. testing water levels for cholera).

4.2 Treatment Plan 2: Vaccinations on Base Model

$$\frac{dS}{dt} = \mu N - \mu S - \beta_i SI - \beta_w SW - \nu S$$
$$\frac{dI}{dt} = \beta_i SI + \beta_w SW - I(\gamma + \mu + \alpha)$$
$$\frac{dR}{dt} = \gamma I - \mu R + \nu S$$
$$\frac{dW}{dt} = \xi I - \sigma W$$

- $\nu =$ is vaccination rate on S class

4.3 Treatment Plan 3: Antibiotics on Base Model

$$\frac{dS}{dt} = \mu N - \mu S - \beta_i SI - \beta_w SW$$
$$\frac{dI}{dt} = \beta_i SI + \beta_w SW - I(\gamma + \eta + \mu + \alpha)$$
$$\frac{dR}{dt} = (\gamma + \eta)I - \mu R$$
$$\frac{dW}{dt} = \xi I - \sigma W$$

- η = is the rate at which individuals recover and leave the I class due to antibiotic tratment

5 Comparing Treatment Strategies For Cholera

5.1 Numerical Simulations and Phase Portraits For The Single Patch Model

5.2 Numerical Simulations and Phase Portraits of Base and Treatment Models

The following are numerical simulations and phase portraits for the base model with vital dynamics, and the three treatment models.

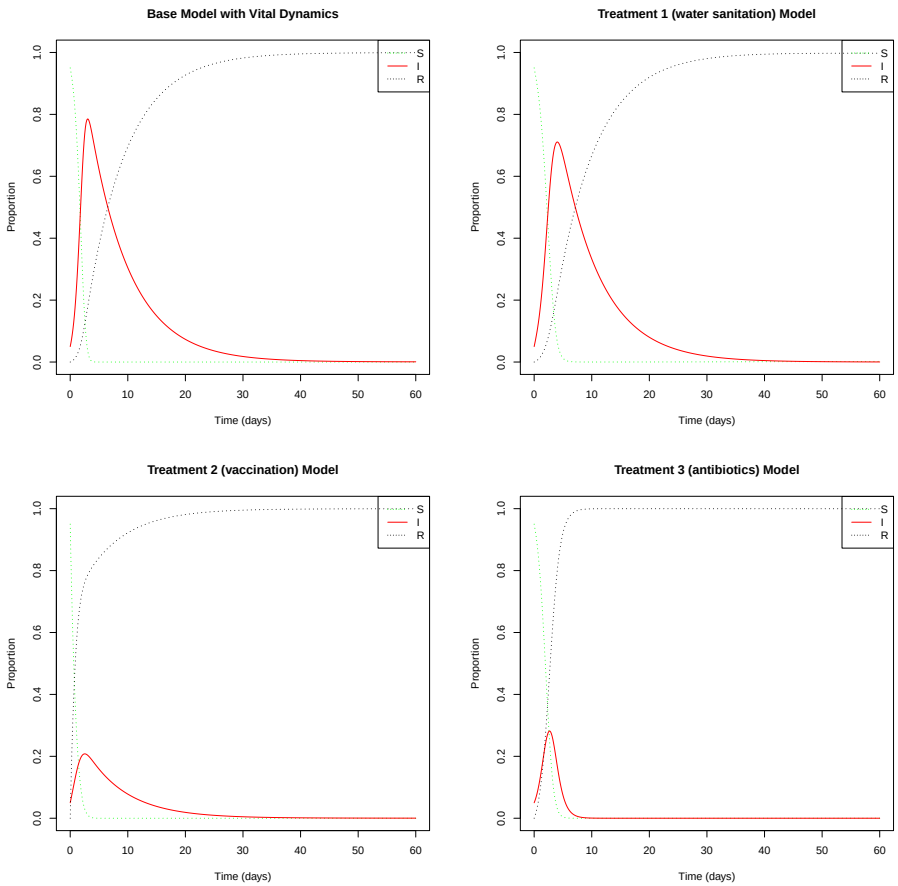

Figure 3: Plot of the SIRW model for a single patch and various treatment models. Parameters are $\mu = 0.15,\ \beta_i = 0.06,\ \gamma = 0.14,\ \sigma = 0.07,\ \beta_w = 0.15,\ \xi = 10,\ \rho = 0.9,\ \nu = 0.9,\ \eta = 0.9,\ \alpha = 0$. The initial conditions for the model were $S_0 = 0.95,\ I_0 = 0.05,\ R_0 = 0$

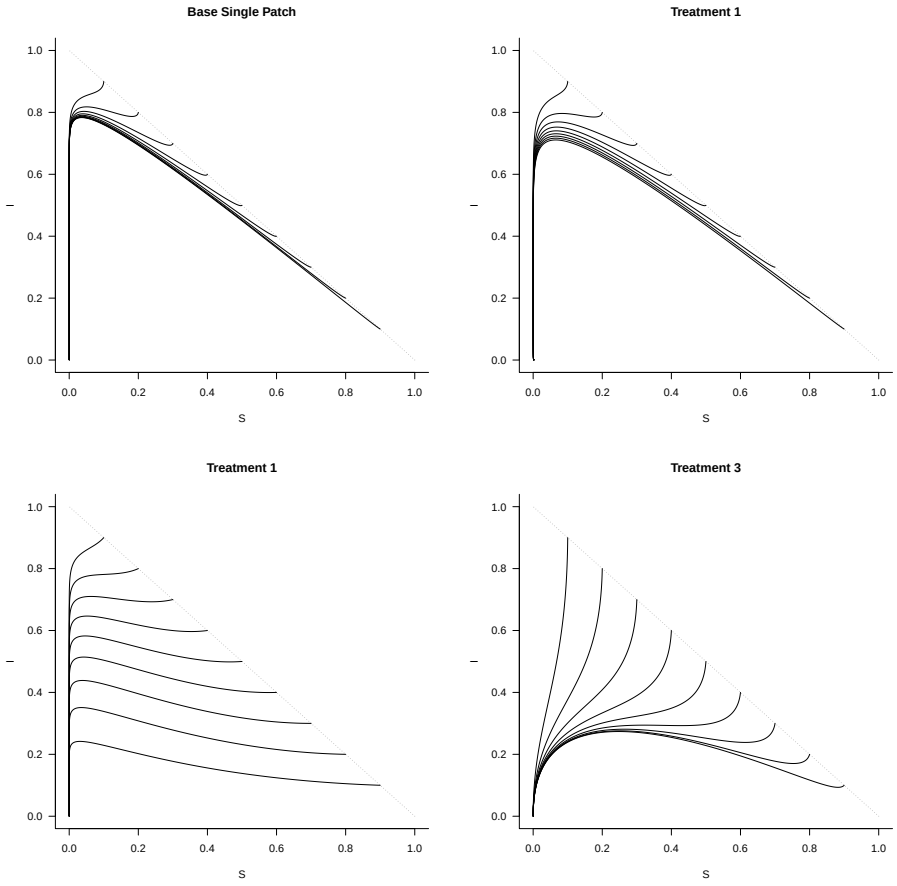

Figure 4: Phase portraits for a single patch and various treatment models. Parameters are $\mu = 0.15,\ \beta_i = 0.06,\ \gamma = 0.14,\ \sigma = 0.07,\ \beta_w = 0.15,\ \xi = 10,\ \rho = 0.9,\ \nu = 0.9,\ \eta = 0.9,\ \alpha = 0$. The initial conditions for the model were $S_0 = 0.95,\ I_0 = 0.05,\ R_0 = 0$

From the phase portraits in figure 4, and the time series in figure 3 it is clear that all treatments appear to have an effect on transmission dynamics, causing the infection to peak at a much higher level of incidence much quicker than without the treatment. However the infectives also appear to recover comparably quickly as well, as seen by the sharp drop off in I. All treatments appear to show very similar effects for the single patch model, but how work in the spatial model may differ, espescially singe the treatments can be applied heterogenously across the patches, in proportion to the initial infectives of each patch.

We hope to compare the effectiveness of these methods by comparing the final size, which can be computed from $\mathcal{R}_0$ in R using Lambert's W function, as noted in the supplementary material of Earn *et al.,* 2014.

$$Z(\mathcal{R}_0) = 1 + \frac{1}{\mathcal{R}_0} W(-\mathcal{R}_0 e^{\mathcal{R}_0}) \tag{1}$$

If similar final sizes are estimated for multiple treatment strategies, then relative costs of the treatments may be compared to decide between them. Cost is not necessairily only monetary, as risk is associted with overuse of antibiotics, water sanitation requires maintenance, all strategies require work from various healthcare or engineering professions. Further work and research needs to be done to define a more formal, specific cost comparison scheme in this case.

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