

Examining Control Strategies for Cholera Incorporating Spatial Dynamics

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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

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1 Background

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 and our assumptions. 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. For simplicity we will assume:

- Natural Birth Rate = Natural Death Rate.
- The population is equally susceptible to infection.
- There is no waning immunity (individuals cannot go back to being susceptible after they recover from cholera).
- There is no latency period (no significant latency period was documented in studies).

- Only infectious individuals can contaminate the water sources by shedding the pathogen into the water.
- The water sources are still.

The halting remedy suggested in 1848 in London 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). Three possible treatment strategies for controlling cholera outbreaks are vaccination, antibiotic treatment, and water sanitation. We will 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 today's 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

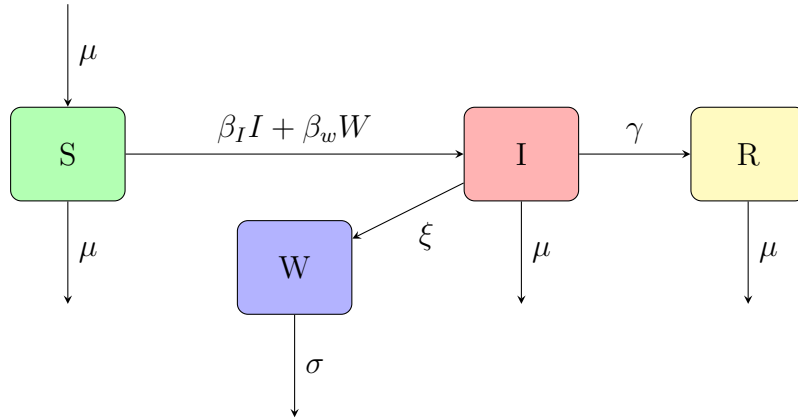
In this paper, we consider the cholera SIWR model as outlined by Tien and Earn Tien & Earn, 2010 with the addition of death rate by cholera σ . The tables below summarize the variables and parameters involved.

	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



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

- 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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## Loading required package: rootSolve
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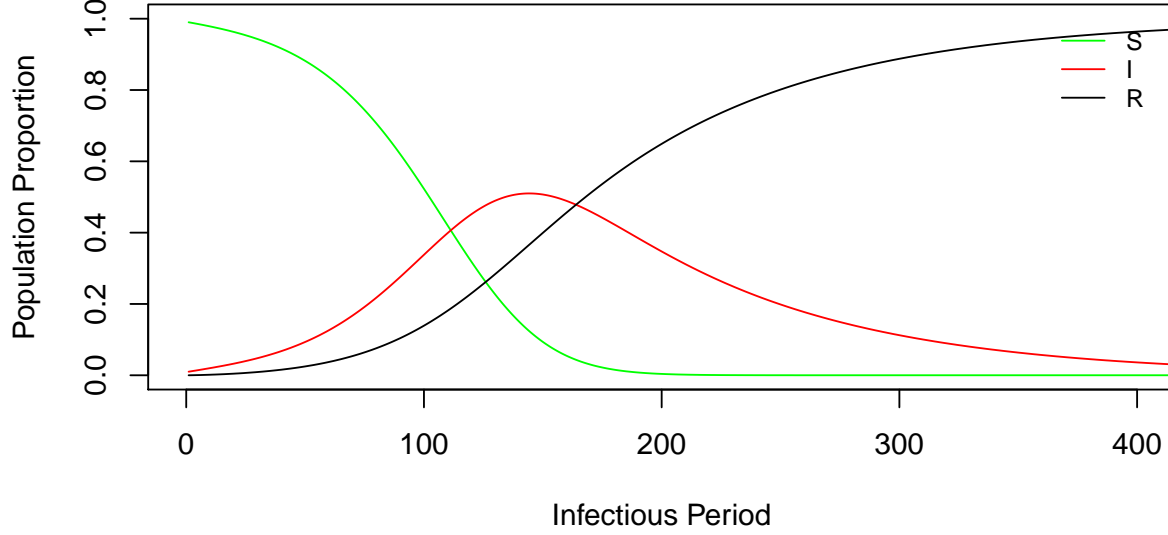


Figure 1: Plot of the SIRW model for a single patch. Parameters are $\mu = 0$ $\beta_I = 0.02$ $\gamma = 0.14$ $\sigma = 0.04$ $\beta_w = 0.5$ $\alpha = 0$ $\xi = 10$. Further the initial conditions for the model were $S_0 = 0.99$ $I_0 = 0.01$ $R_0 = 0$.

131 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

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

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

2.4 Single Patch With Low And High Shedding Compartments

$$\begin{aligned}\frac{dS}{dt} &= \mu N - \mu S - \beta_L SI_L - \beta_H SI_H - \beta_w SW \\ \frac{dI_L}{dt} &= \beta_i S(I_L + I_H) + \beta_w SW - I_L(\mu + \delta + \alpha_L) \\ \frac{dI_H}{dt} &= \delta I_L - I_H(\gamma + \mu + \alpha_H) \\ \frac{dR}{dt} &= \gamma I_H - \mu R \\ \frac{dW}{dt} &= \xi_L I_L + \xi_H I_H - \sigma W\end{aligned}$$

This model assumes that you start off with low intensity symptoms (lower rate of shedding) and the symptoms reach a high intensity with a greater rate of shedding. The assumptions for the single patch model apply here as well.

- α_L = death rate by cholera for low intensity infected
- α_H = death rate by cholera for high intensity infected
- ξ_L = Shedding rate of cholera into water for low intensity infectives
- ξ_H = Shedding rate of cholera into water for high intensity infectives
- δ = Transition rate from low intensity to high intensity infection

3 Multi Patch Model

The multimodel patch is represented as a square matrix of single patch models, with equations governing the diffusion of each population compartment between patches. The following equations represent the SIRW model for a set of patches where S, I, R, W are all N by N

sqaure matrices

$$\begin{aligned}\frac{dS}{dt} &= \mu N - \mu S - \beta_i SI - \beta_w SW + D(S, M_S) \\ \frac{dI}{dt} &= \beta_i SI + \beta_w SW - I(\gamma + \mu + \alpha) \\ \frac{dR}{dt} &= \gamma I - \mu R + D(R, M_R) \\ \frac{dW}{dt} &= \xi I - \sigma W + D(W, M_W)\end{aligned}$$

- 144 • μ = natural death rate
 - 145 • β_i = transmission rate between S and I class
 - 146 • β_w = transmission rate between I and W class
 - 147 • γ = recovery rate (I to R class)
 - 148 • α = death rate from cholera
 - 149 • ξ = Shedding rate of cholera from I to W class
 - 150 • σ = Removal rate of cholera from W class (depends on what we define as our water
 - 151 source)
 - 152 • M_S The dispersal rate of succceptibles between patches
 - 153 • M_R = The dispersal rate of recovered people between patches
 - 154 • M_W = The dispersal rate of water between patches
- 155 The assumptions for the single patch model apply here as well as the following:
- 156 • No dispersal of infected individuals between patches
 - 157 • All patches have the same parameter values

The function $D(C, M_C)$ is defined as

$$\begin{aligned}\frac{\partial C}{\partial t} &= -\frac{1}{A} \cdot \frac{\partial A \cdot J}{\partial x} \\ J &= -M_C \cdot \frac{\partial C}{\partial x}\end{aligned}$$

158 Where the varaibles are

- 159 • A is the total surface area of the region
- 160 • C C is the fraction of the patch population in that compartment
- 161 • x is space

162 • t is time

163 • J are the fluxes of each patch

164 • M_C is the diffusion coefficient

165 Distance between adjacent patches is arbitrarily defined to be 0.3, thus $A = (0.3)^2 \cdot rows \cdot$
166 $columns$, which is the area of then entire square region containing all patches.

167

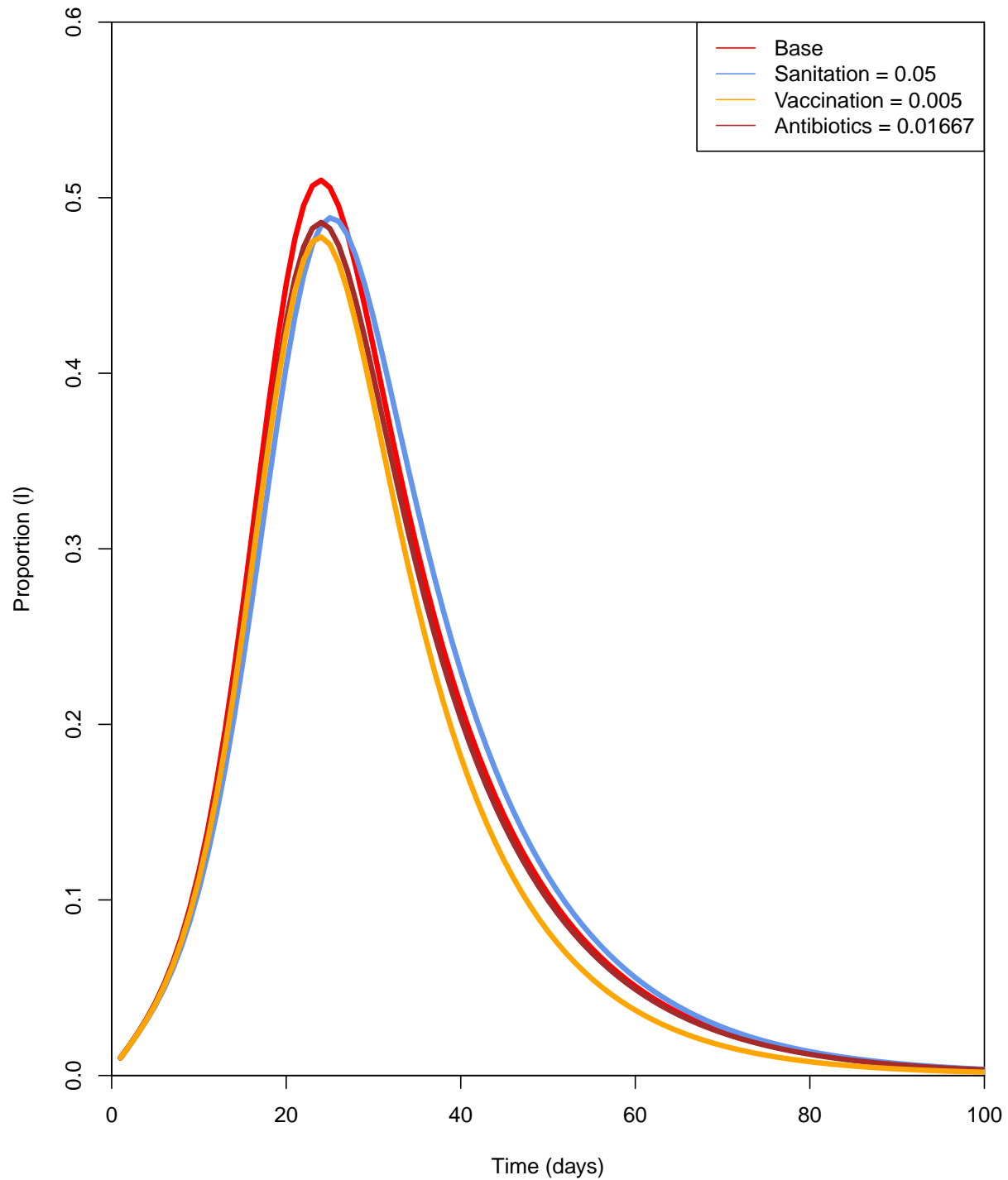


Figure 2: Plot comparing treatments for the single patch SIRW model. The parameter values are $\mu = 7e - 05$, $\beta_i = 0.025$, $\gamma = 0.14286$, $\sigma = 0.04$, $\beta_w = 0.5$, $\xi = 10$, $\alpha = 0$. The initial conditions for the model were $S_0 = 0.99$, $I_0 = 0.01$, $R_0 = 0$.

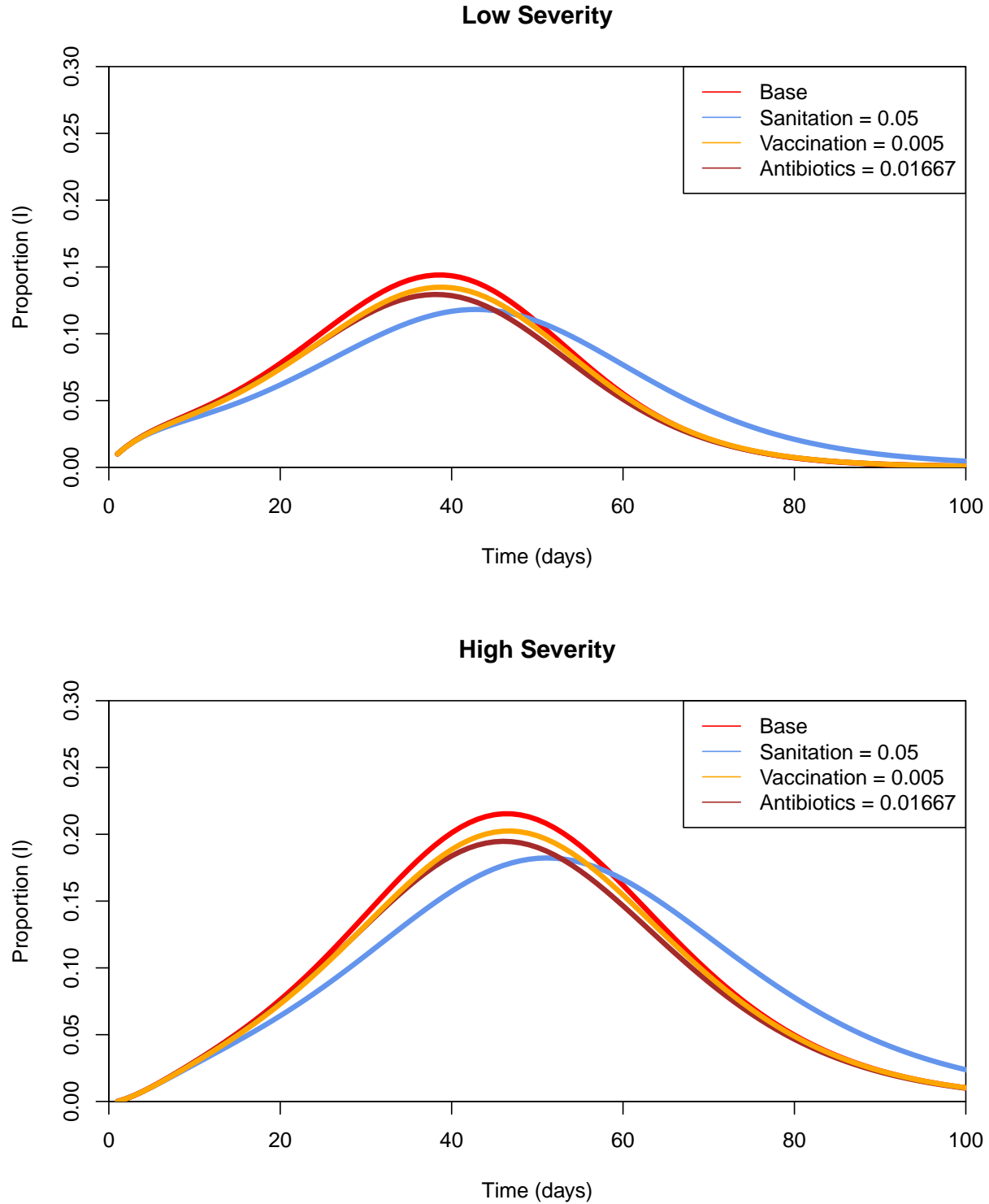


Figure 3: Plot of different treatments for the single patch model with high and low severity infectives. The parameter values are $\mu = 7e - 05$, $\beta_l = 0.016$, $\beta_h = 0.016$, $\gamma = 0.14286$, $\sigma = 0.04$, $\beta_w = 0.5$, $\xi_l = 0.07$, $\xi_h = 0.14$, $\alpha_l = 0.01$, $\alpha_h = 0.05$. The initial conditions for the model were $S_0 = 0.99$, $I_0 = 0.01$, $R_0 = 0$.

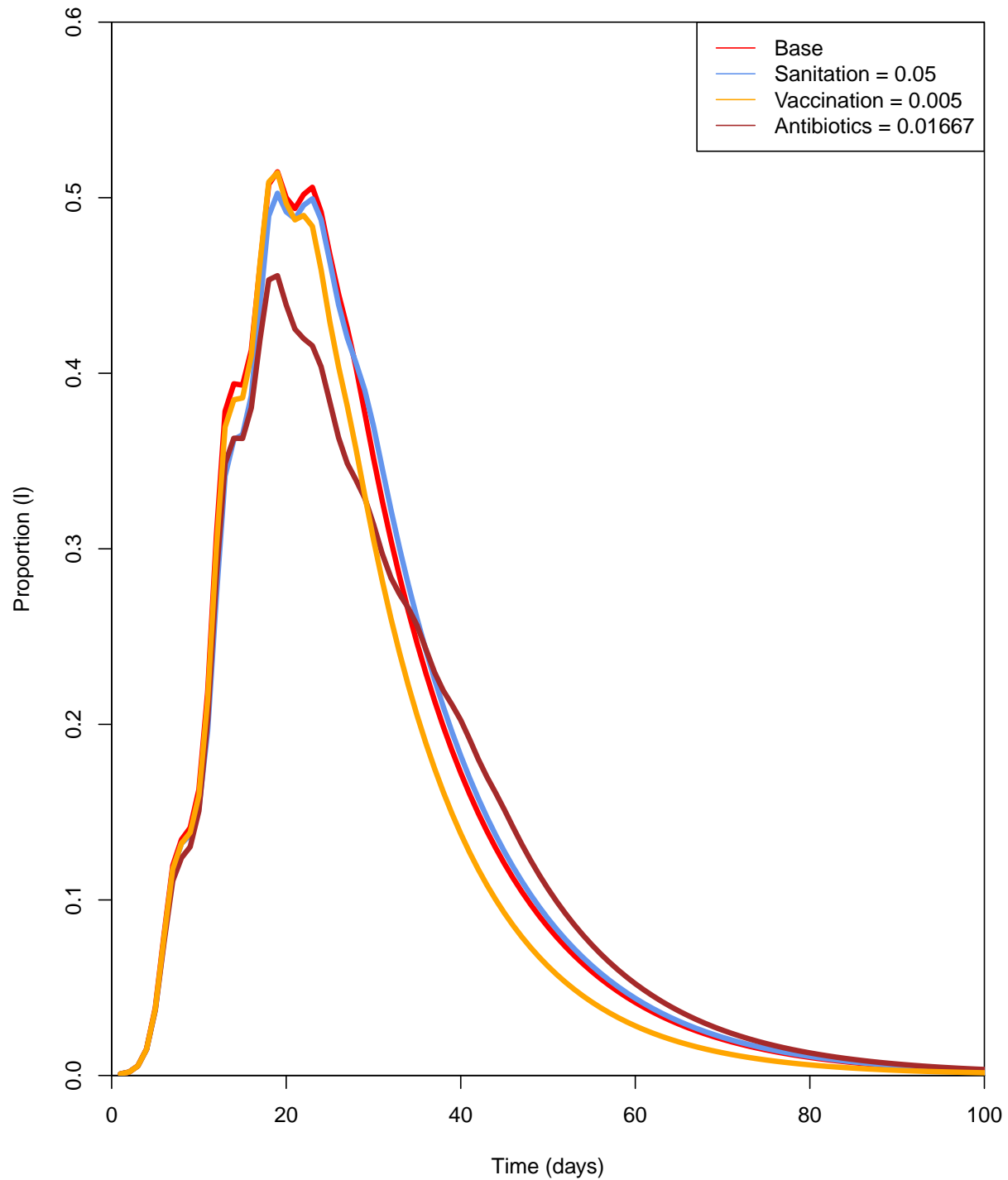


Figure 4: Plot comparing treatments for the multipatch SIRW model. The parameter values are $\mu = 7e - 05$, $\beta_i = 0.025$, $\gamma = 0.14286$, $\sigma = 0.04$, $\beta_w = 0.5$, $\xi = 10$, $\alpha = 0$. The initial conditions for the model were $S_0 = 0.99$, $I_0 = 0.01$, $R_0 = 0$.

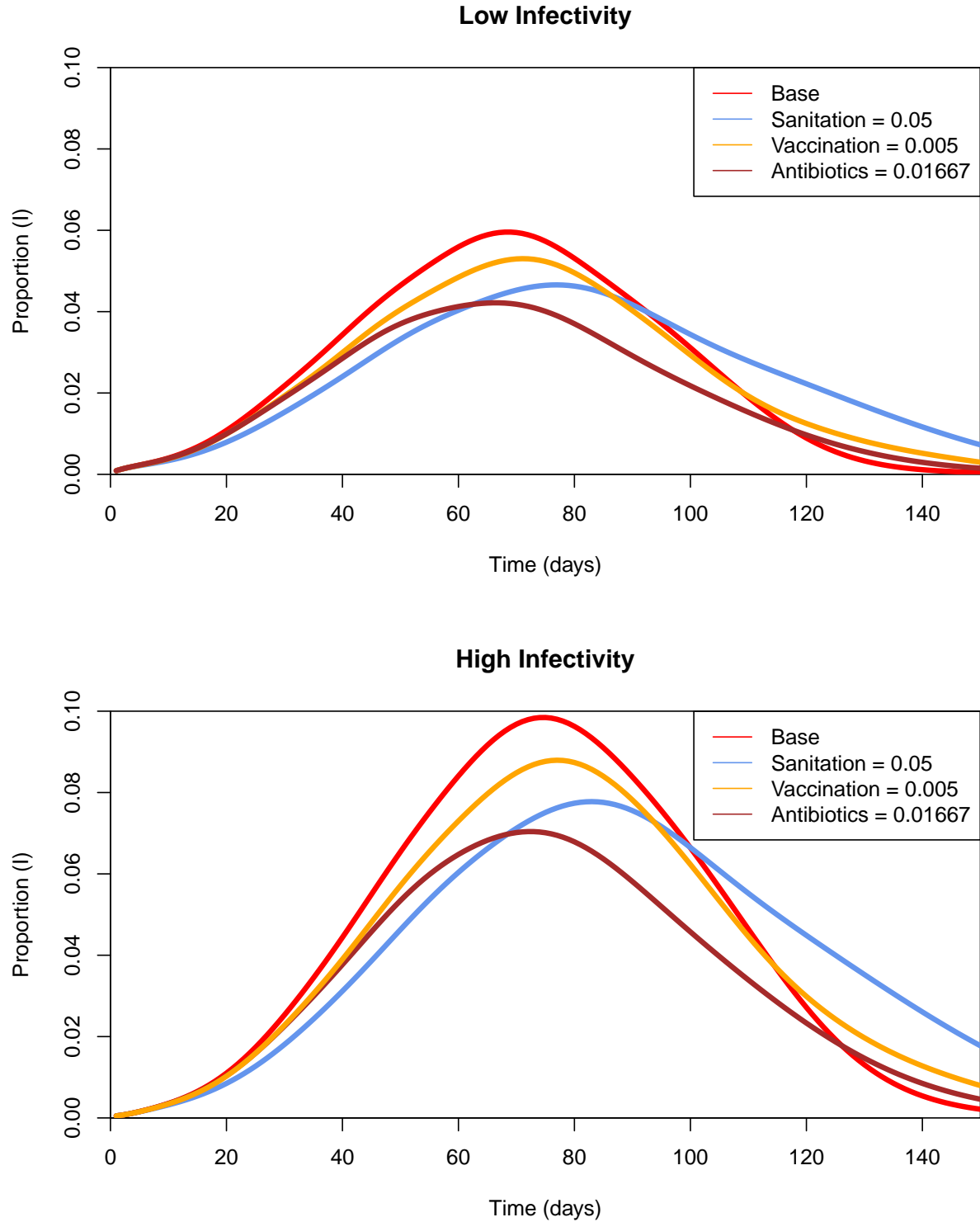


Figure 5: Plot of different treatments for the multipatch model with high and low severity infectives. The parameter values are $\mu = 7e - 05$, $\beta_l = 0.016$, $\beta_h = 0.016$, $\gamma = 0.14286$, $\sigma = 0.04$, $\beta_w = 0.5$, $\xi_l = 0.07$, $\xi_h = 0.14$, $\alpha_l = 0.01$, $\alpha_h = 0.05$. The initial conditions for the model were $S_0 = 0.99$, $I_0 = 0.01$, $R_0 = 0$.

4 Treatment Strategies For Cholera

The three treatments that will be analyzed in regard to the single SIWR model are water treatment, vaccination, and antibiotics. The results of the analysis will aid government officials in implementing intervention strategies by determining optimal parameters (that represent the different intervention strategies) that would be most effective in lowering the estimated reproductive number \mathcal{R}_0 , peak prevalence, and the final size.

4.1 Treatment Plan 1: Sanitation of water over time

Water, sanitation, and hygiene (WASH) intervention is the most simplest and one of the effective ways of to reduce the spread of cholera. One of the easiest ways to implement intervention strategies that is easily quantifiable and measurable is through water sanitation via chlorination and filtration of water sources (Taylor *et al.*, 2015). In the following model, a water treatment strategy would affect the water compartment (essentially increasing the removal or death rate of bacteria in water). This can be implemented as a new term ρ .

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

For example, ρ can either be a constant, or dependent on I or W :

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

ρ represents the sanitation (increased removal of cholera) rate of λ , implemented at certain threshold of infected (in this case the threshold is based on I but can be based on W (i.e. testing water levels for cholera). For model simplicity, ρ will be regarded as a constant term and can viewed as a sanitation rate. The biologically plausible range for this parameter is $0 \leq \rho \leq 1$.

In addition to the base model assumptions, this treatment model assumes that treatment of water only affects the concentration of cholera bacteria within water reservoirs which are the only source of water for the population.

4.2 Treatment Plan 2: Vaccinations on Base Model

Cholera vaccine injections were first invented in 1885 and were first used during the mass vaccination campaigns of the Spain outbreaks (Mukerjee, 1963). Biotechnological advances

in the late 20th century have resulted in the creation of immunization via oral cholera vaccines (OCV) which are more effective than their injective equivalent but require two stage dose administration with immunity imparted after one week after the first dose (Mukerjee, 1963) (Fung *et al.*, 2013). Although the London outbreaks occurred prior to the creation of the vaccine, creating a model that implements vaccination techniques is vital for modelling future cholera outbreaks and can be further analyzed to determine the effect on \mathcal{R}_0 and the final size of the epidemic.

This model assumes that vaccination is applied to the susceptible population and not before introduction into the system; this is done instead of vaccination at birth before entry into system since the cholera vaccine is not administered during infancy (Fung *et al.*, 2013).

This model also assumes that the vaccine targets the only strain of the cholera bacteria that has caused the epidemic. It is possible that new strains of cholera can create a reccuring endemic (herald waves) with seasonality as described in Tien et al. (Tien, Poinar, *et al.*, 2011).

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

- ν = is vaccination rate on S class

4.3 Treatment Plan 3: Antibiotics on Base Model

More modern techniques of treating cholera involve the use of antibiotics. Several antibiotics that are regarded as effective against cholera such as azithromycin have been used since the early 1990s (Nelson *et al.*, 2011). Use of antibiotics when infected effectively shortens the duration of diarrhea and results in fewer bowel movements and lower stool volume (Saha *et al.*, 2006). This biological process can be either be implemented in the base single patch model by lowering the duration of the infectious period (which can be be viewed as an introduction of a new parameter in dI/dt) or by lowering the shedding rate into water (which can be implemented by lowering the shedding rate ξ). The following model implements a

229 decrease in the duration of the infectious period by using the term $-\eta I$.

$$\begin{aligned}
 230 \quad & \frac{dS}{dt} = \mu N - \mu S - \beta_i SI - \beta_w SW \\
 231 \quad & \frac{dI}{dt} = \beta_i SI + \beta_w SW - I(\gamma + \eta + \mu + \alpha) \\
 232 \quad & \frac{dR}{dt} = (\gamma + \eta)I - \mu R \\
 233 \quad & \frac{dW}{dt} = \xi I - \sigma W
 \end{aligned}$$

234
235

- 236 • η = is the rate at which individuals recover and leave the I class due to antibiotic
237 treatment

238 5 Comparing Treatment Strategies For Cholera

239 5.1 Numerical Simulations and Phase Portraits For The Single 240 Patch Model

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

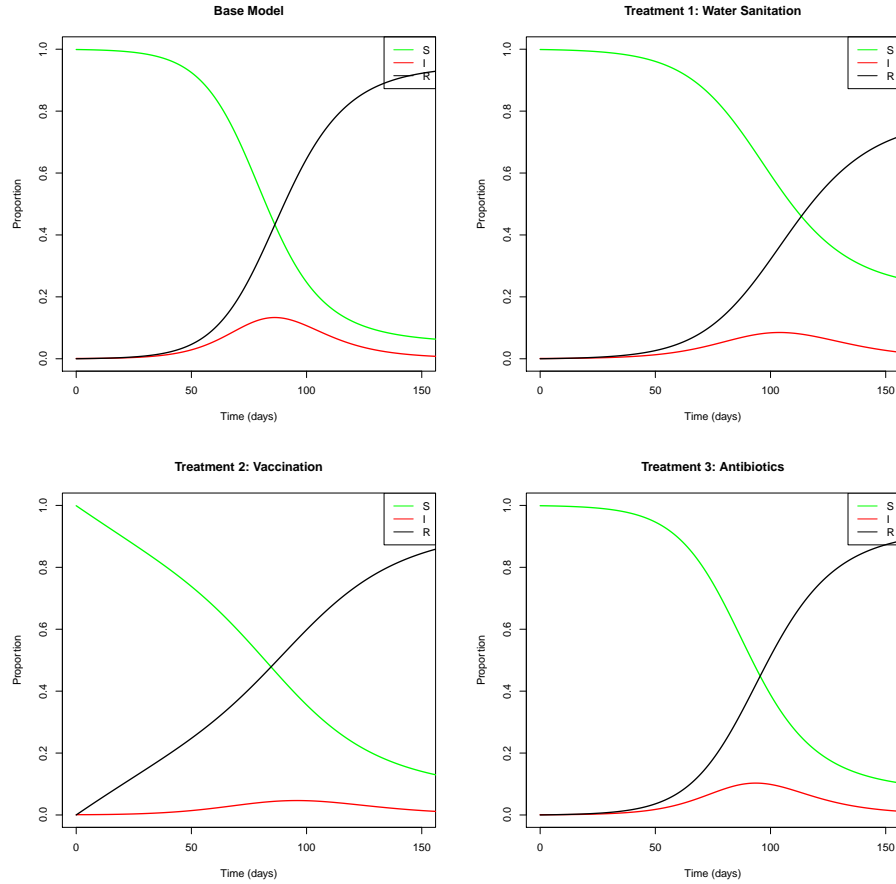


Figure 6: Plot of the SIRW model for a single patch and various treatment models. Parameters are $\mu = 6.50618087182824e - 05$, $\beta_i = 0.025$, $\gamma = 0.14$, $\sigma = 0.04$, $\beta_w = 0.5$, $\xi = 10$, $\rho = 0.05$, $\nu = 0.005$, $\eta = 0.01667$, $\alpha = 0$. The initial conditions for the model were $S_0 = 0.99$, $I_0 = 0.01$, $R_0 = 0$

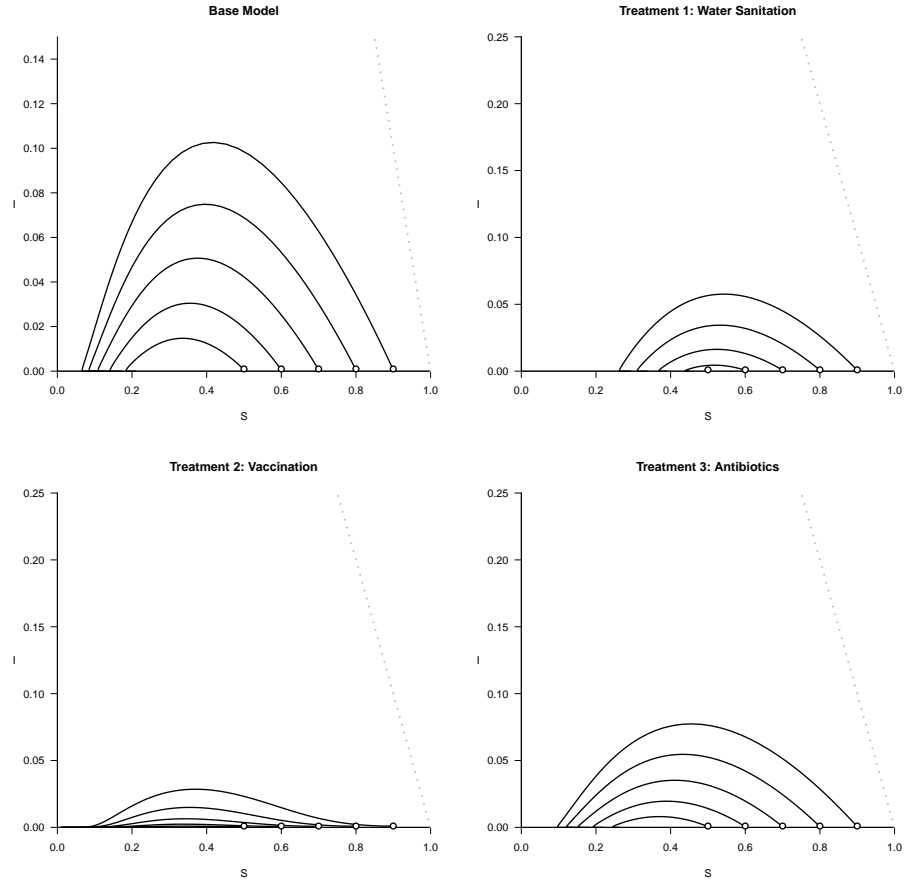


Figure 7: Phase portraits for a single patch and various treatment models. Parameters are $\mu = 6.50618087182824e - 05$, $\beta_i = 0.025$, $\gamma = 0.14$, $\sigma = 0.04$, $\beta_w = 0.5$, $\xi = 10$, $\rho = 0.05$, $\nu = 0.005$, $\eta = 0.01667$, $\alpha = 0$. The initial conditions for the model were $S_0 = 0.99$, $I_0 = 0.01$, $R_0 = 0$

From the phase portraits in figure 7, and the time series in figure 6 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, especially since the treatments can be applied heterogeneously 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.

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

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 necessarily only monetary, as risk is associated 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.

5.2 Treatment Model Discussion

When comparing the treatments solely based on \mathcal{R}_0 and the final size, it is easy to overlook the practicality of each treatment. WASH intervention is the simplest treatment technique, with hygiene and clean water distribution usually the first treatment implementation at the start of an outbreak. Chlorination techniques have had a few pitfalls depending on the quality of implementation. Well chlorination with liquid bleach which was used during the 2008 cholera outbreak in Guinea Bissau was considered ineffective in maintaining the recommended free residual chlorine amount, whereas the use of chlorinators (slow releasing chlorine tablets) depends on the maintenance by surrounding citizens (link27). In terms of pragmatism, it is impractical to only implement antibiotic prophylaxis to those who are infected as well as those who come in contact with the contaminated water source (since mass antibiotic implementation would increase the chance of selecting antibiotic resistant strains) (Nelson *et al.*, 2011).

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References

1. Codeco, C. T. Endemic and epidemic dynamics of cholera: the role of the aquatic reservoir. *BMC Infect. Dis.* **1**, 1 (2001).
2. Earn, D. J., Andrews, P. W. & Bolker, B. M. Population-level effects of suppressing fever. *Proc. Biol. Sci.* **281**, 20132570 (Mar. 2014).
3. Fung, I. C., Fitter, D. L., Borse, R. H., Meltzer, M. I. & Tappero, J. W. Modelling the effect of water, sanitation, and hygiene and oral cholera vaccine implementation in Haiti. *Am. J. Trop. Med. Hyg.* **89**, 633–640 (2013).
4. Grad, Y. H., Miller, J. C. & Lipsitch, M. Cholera modeling: challenges to quantitative analysis and predicting the impact of interventions. *Epidemiology* **23**, 523–530 (2012).
5. Kaper, J. B., Morris, J. G. & Levine, M. M. Cholera. *Clinical Microbiology Reviews* **8**, 48–86 (1995).
6. Moe, C. L. & Rheingans, R. D. Global challenges in water, sanitation and health. *J Water Health* **4 Suppl 1**, 41–57 (2006).
7. Mukerjee, S. Preliminary studies on the development of a live oral vaccine for anti-cholera immunizaion. *Bull. World Health Organ.* **29**, 753–766 (1963).
8. Nelson, E. J., Nelson, D. S., Salam, M. A. & Sack, D. A. Antibiotics for both moderate and severe cholera. *N. Engl. J. Med.* **364**, 5–7 (2011).
9. Paneth, N., Vinten-Johansen, P., Brody, H. & Rip, M. A rivalry of foulness: official and unofficial investigations of the London cholera epidemic of 1854. *Am J Public Health* **88**, 1545–1553 (1998).
10. Saha, D., Karim, M. M., Khan, W. & Ahmed, S. Single-dose azithromycin for the treatment of cholera in adults. *N. Engl. J. Med.* **364**, 2452–2462 (2006).
11. Taylor, D., Kahawita, T., Cairncross, S. & Ensink, J. H. J. The Impact of Water, Sanitation and Hygiene Interventions to Control Cholera: A Systematic Review. *PLoS ONE* **10** (2015).
12. Tien, J. H. & Earn, D. J. Multiple transmission pathways and disease dynamics in a waterborne pathogen model. *Bull. Math. Biol.* **72**, 1506–1533 (2010).
13. Tien, J. H., Poinar, H. N., Fisman, D. N. & Earn, D. J. Herald waves of cholera in nineteenth century London. *J R Soc Interface* **8**, 756–760 (2011).
14. WHO. *Cholera* <https://www.who.int/news-room/fact-sheets/detail/cholera> (2019).