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MODELING THE EFFECT OF VACCINES ON CHOLERA TRANSMISSION

URMI GHOSH-DASTIDAR*
Department of Mathematics
New York City College of Technology, CUNY
Namm 711, 300 Jay St., Brooklyn, NY 11201, USA
**ughosh-dastidar@citytech.cuny.edu*

SUZANNE LENHART
Department of Mathematics
University of Tennessee Knoxville
TN 37996-1300, USA
lenhart@math.utk.edu

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Cholera is a diarrhoeal disease that is caused by an intestinal bacterium, *Vibrio cholerae*. Recently an outbreak of cholera in Haiti brought public attention to this deadly disease. In this work, the goal of our differential equation model is to find an effective optimal vaccination strategy to minimize the disease related mortality and to reduce the associated costs. The effect of seasonality in pathogen transmission on vaccination strategies was investigated under several types of disease scenarios, including an endemic case and a new outbreak case. This model is an extension of a general water-borne pathogen model. This work involves the optimal control problem formulation, analysis and numerical simulations.

Keywords: Pathogens; Optimal Control; Objective Functional; SIWR Model.

1. Introduction

Recently, an outbreak of cholera in Haiti brought public attention to this deadly disease. Cholera is a diarrhoeal disease caused by an intestinal bacterium, *Vibrio cholerae*. In October 2010, the Center of Disease Control (CDC) confirmed the existence of the pathogenic bacteria *Vibrio cholerae* O_1, serotype Ogawa, biotype E_1 in Haiti. According to the CDC, once this bacteria was confirmed in Haiti on 21 October 2010, surveillance data collected through 3 December and provided by the Haitian Ministry of Public Health and Population (MSPP) confirmed that a cholera

*Corresponding author.

outbreak had spread everywhere in the nation.[1,2] As of 17 October 2013, there were 684,085 reported cases of cholera; 380,846 (55.4%) patients had been hospitalized and 8,361 deaths were reported since the cholera outbreak was first reported. The United Nations (UN) estimated that about 3,000 people died from cholera infection during a 2008 outbreak at Zimbabwe.[3] Cholera epidemics usually occur in underdeveloped areas that lack proper hygiene and sanitation, and have limited access to clean water. The World Health Organization (WHO) recognizes cholera as a global threat to public health; it reports a significant increase in the number of cholera cases and outbreaks with new profiles in places where the disease had not been present for several years. Thus, this disease is considered a re-emerging disease.[4] Though cholera outbreaks are not common in developed countries, handling an outbreak remains a major challenge in both developing and underdeveloped countries once the disease has its first onset.

The pathogenic bacterium, *Vibrio cholera*, is found in the feces of infected people. It is usually spread when an infected person sheds pathogens into the drinking water or contaminates food. Most reported cases of person-to-person transmission occur in households. This can happen if a person interacting with an infected person also gets involved with food preparation.[5–7] In 2003–2004 in Lusaka, Zambia, a cholera epidemic caused an enormous loss of lives when the disease was spread through contaminated raw vegetables that had come into contact with an infected person.[8] This is not an unlikely event if an infected person is asymptomatic or is in the early stages when the disease is yet to be detected.

Neilan *et al.*[9] investigated optimal intervention strategies for regulating cholera transmission during an outbreak. In their model of differential equations, susceptible individuals became infected through ingestion of bacteria-contaminated water at two different rates based on the infectiousness of the particular *vibrios*. Two infected classes were used, asymptomatic and symptomatic. Immunity to cholera was assumed to be temporary. The model included three different control intervention strategies: combined rehydration and antibiotic treatment, vaccination, and sanitation. The optimal control results of this system of differential equations used cholera data available from Bogra and Calcutta, India. One of the significant findings of this study was that immediate vaccination is a cost-effective method of minimizing death by preventing severe infections.

Tien and Earn[10] formulated a differential equations model with *SIR* compartments for disease dynamics of waterborne pathogens through multiple pathways. An additional compartment W (*SIWR*) was added to monitor pathogen concentrations in water to address the dynamics of disease transmission that occurs through multiple transmission routes. This model assumed a constant population size within the time-frame of the study period and also assumed that susceptible individuals can be infected either by personal contact with infected individual or through water that is contaminated by contaminated human feces. A follow-up paper by Tien *et al.*[11] showed application of this model, in a slightly revised form to describe cholera propagation of herald waves in 19th century London. A seasonality term for

waterborne pathogen transmission was used to describe seasonal nature of cholera transmission; the cholera data showed that high mortality almost always occurs in summer.

Tuite *et al.*[12] used a gravity model to describe regional cholera epidemics in Haiti, in which the between-region epidemic spread was dependent on population sizes and the distance between regional centroids. It incorporated intervention strategies such as vaccination and provision of clean water. Vaccination strategies were discussed based on three cases: equal allocation to different Haitian departments, allocation based on population proportion, and optimization.

A cholera model was developed by Wang and Liao[13] that is primarily based on the classical SIR model with an additional environmental component. Shuai *et al.*[14] developed a model to describe cholera transmission that incorporates hyperinfectivity in *vibrios* and temporary immunity classes and that uses distributed delays. Stability of the endemic equilibrium was studied and numerical results illustrated the effects of hyperinfectivity and temporary immunity on disease oscillations.

A new cholera model with multiple patches (various populations) with nonlinear incidence functions and temporary immunity was proposed that considered both water and human movement between patches. The type/target reproduction numbers were also defined and derived to measure various control strategies that were needed for disease eradication from all patches.[15] An examination of rainfall and cholera dynamics in Haiti using statistical and dynamic modeling approaches showed strong correlation between rainfall and cholera incidence for all spatial scales and locations that were being studied.[16] A multiple transmission model of cholera was built by using multiple patches with direct transmission occurring within patch while indirect transmission occurring between patches via a single shared water source. Effect of heterogeneity was studied under dual transmission pathways. Disease dynamics is first described by using a 2-patch (two populations) SIWR model with shared water source and then it was extended to an n-patch model.[17]

Currently, there are two types of vaccinations available for cholera — Dukoral (manufactured by SBL vaccines) and ShanChol (manufactured by Shantha Biotec in India). A person requires two doses of vaccine to be fully protected. However, multiple weeks may pass before persons receiving the vaccine are fully protected.

We use optimal control theory to investigate vaccination strategies in an extension of the SIWR model. We investigate the effect of seasonality in the water compartment on the optimal vaccination strategies. Our model is presented in the next section together with our optimal control formulation. Some numerical examples are given to illustrate specific cases in Sec. 3.

2. Model and Optimal Control Formulation

The objective of this project is to find an effective optimal vaccination strategy to minimize disease related mortality and to reduce associated costs. We start with the SIWR model proposed by Tien and Earn.[10] The SIWR (Susceptible

S–Infectious I–Waterborne Pathogen Concentration W–Recovered R) model is modified by adding terms with vaccination (V), an immunity loss term for recovered population (rate ω), and a d term with the disease related death (rate d). The control function $V(t)$ represents the rate of susceptible individuals being vaccinated per unit of time. We assume the infection is transmitted mainly via the waterborne pathogens at rate b_W; however, it can spread through person-to-person contacts with rate b_I. The natural birth and death rates, respectively, are given as n and μ. Only those persons who receive two-doses of vaccines are included in the recovered class. However, we do not explicitly consider the two-dose situation for vaccine. Additionally, we assume the vaccine provides the same strength of immunity as had by those individuals who have recovered. All immunity to cholera is assumed to wane at rate ω. All disease related recoveries occur at rate γ. Furthermore, the infected individuals are assumed to shed pathogens in water at rate α and pathogens decay in water at rate ξ. We have not considered asymptomatic individuals. Our state system with states S, I, W, and R is given by:

$$\begin{aligned}
\frac{dS}{dt} &= n(S+I+R) - b_W WS - b_I SI - V(t)S - \mu S + \omega R,\\
\frac{dI}{dt} &= b_W WS + b_I SI - \gamma I - \mu I - dI,\\
\frac{dW}{dt} &= \alpha I - \xi W,\\
\frac{dR}{dt} &= \gamma I + V(t)S - \mu R - \omega R.
\end{aligned} \tag{2.1}$$

It is important to find an optimal strategy to vaccinate the population if an outbreak occurs. Our goal is to find an effective intervention strategy for minimizing the number of infected persons and the overall cost of the vaccine during a fixed time period. Our objective functional to be minimized is:

$$\int_0^T (AI + B_1 VS + B_2 V^2)dt, \tag{2.2}$$

where A, B_1, and B_2 are weight parameters giving the relative level of importance of variables in the objective functional. This objective functional is minimized over the control set U where

$$U = \{V \in L^\infty(0,T) \,|\, 0 \le V(t) \le V_{\max} \text{ a.e. t}\}.$$

The units of those parameters can transform the integral into dollars. The final time T is given in days. Note that the system is only influenced by the ratio of the constants $\frac{A}{B_2}$ and $\frac{B_1}{B_2}$ and not by the individual values of these parameters. The first term $\int_T^0 AIdt$ represents the total cost associated with infections. The terms B_1 and B_2 represent the cost of implementing the controls. The term $B_1 VS$ represents part of the cost of vaccinating a certain fraction of the susceptible population whereas,

the quadratic term B_1V^2 of the control variable represents the nonlinear part of the cost. See Ref. 18 for an explanation of such nonlinear cost terms.

Using Pontryagin's Maximum Principle,[19] the Hamiltonian H is given by:

$$\begin{aligned} H = {} & AI + B_1 VS + B_2V^2 \\ & + \lambda_S[n(S+I+R) - b_W WS - b_I SI - VS - \mu S + \omega R] \\ & + \lambda_I[b_W WS + b_I SI - \gamma I - \mu I - dI] \\ & + \lambda_W[\alpha I - \xi W] + \lambda_R[\gamma I + VS - \mu R - \omega R]. \end{aligned} \tag{2.3}$$

The term $AI + B_1 VS + B_2V^2$comes from the integrand and all other terms come from multiplying the adjoint functions by the right-hand side of the corresponding state differential equation. Note that the structure of our optimal control problem gives existence to an optimal control by standard results like in Ref. 9. Given an optimal vaccination strategy V^*, the following is the set of necessary conditions for minimizing H with respect to V:

$$\begin{aligned} \lambda_j'(t) &= -\frac{\partial H}{\partial x_j}, \quad \lambda_j(T) = 0, \quad x_j = S, I, W, R, \\ \lambda_s'(t) &= -[B_1V + \lambda_s(n - b_W W - b_I I - V - \mu) + \lambda_I(b_W W + b_I I) + \lambda_R V], \\ \lambda_I'(t) &= -[A + \lambda_s(n - b_I S) + \lambda_I(b_I S - \gamma - \mu - d) + \lambda_W \alpha + \lambda_R \gamma], \\ \lambda_W'(t) &= -[\lambda_S(-b_W S) + \lambda_I b_W S - \lambda_W \xi], \\ \lambda_R'(t) &= -[\lambda_s(n + \omega) - \lambda_R(\mu + \omega)]. \end{aligned} \tag{2.4}$$

Note that the Hamiltonian is minimized with respect to the control at $V^*$and this gives

$$\begin{aligned} &\frac{\partial H}{\partial V} = 0 \quad \text{when } 0 < \hat{V}(t) < V_{\max}, \\ &B_1 S + 2B_2\hat{V} - \lambda_S S + \lambda_R S(t) = 0, \\ &S(B_1 - \lambda_S + \lambda_R) = -2B_2\hat{V}, \\ &\hat{V}(t) = \frac{(\lambda_S - \lambda_R - B_1)S(t)}{2B_2}. \end{aligned} \tag{2.5}$$

As in Ref. 12, we choose $V_{\max} = 0.04$. Therefore, an optimal control is characterized as follows:

$$V^*(t) = \max\left(0, \min\left(\frac{(\lambda_S - \lambda_R - B_1)S(t)}{2B_2}, V_{\max}\right)\right). \tag{2.6}$$

The optimality system to be solved numerically involves the state system, the adjoint system, and the control function characterization. Note that the state variables have initial conditions and the adjoint variables have final values. Therefore, an algorithm, the "forward–backward sweep method"[19] is used to solve the optimal control problem. Starting with an initial set of values for the state variables and

an initial guess for the control function over the entire time interval, this method solves the system of state variables forward in time. Next, the method uses the final conditions of the adjoint system, the values of the control function, and the current values of the state variables to solve the adjoint system backward in time. It then updates the new control function value using a convex combination of the old control and the control characterization. This process is repeated until the solution converges.

One can show that the optimal control is unique for a small final time with techniques similar to Ref. 20. In our numerical results, we found no indication of non-uniqueness of optimal controls.

3. Optimal Control Numerical Results

The descriptions of parameters and their values are presented in Table 1. The control problem is run for two different sets of initial conditions: when the disease first starts in a community and when the disease is already endemic. The immunity

Table 1. Parameter values of the cholera model.

Parameters	Definition	Units	Endemic	Introduced	References
n	Natural birth rate	day^{-1}	0.044/365	0.044/365	17
μ	Natural death rate	day^{-1}	0.033/365	0.033/365	17
ω	Immunity waning rate	day^{-1}	0.7/365	0.7/365	12
γ	Recovery rate	individuals^{-1} day^{-1}	$\frac{1}{3} \approx 0.3$	$\frac{1}{3} \approx 0.3$	17
d	Disease-related death rate (symptomatic)	individuals^{-1} day^{-1}	4.662/365	4.662/365	17
α	Rate of pathogen shedding into reservoir	cells ml^{-1} day^{-1} individuals^{-1}	$\frac{3650}{365} = 10$	$\frac{3650}{365} = 10$	17
ξ	Mean pathogen lifetime in water reservoir	day^{-1}	1/14	1/7	17
A'	Amplitude of seasonality of $b_W(t)$	—	0.5	0.88	17
B'	Average value of $b_W(t)$	ml cells^{-1} day^{-1}	$\frac{3.9 \times 10^{-5}}{365}$	$\frac{2.14 \times 10^{-5}}{365}$	17
b_I	Transmission rate for person-to-person	individuals^{-1} day^{-1}	$\frac{9.12 \times 10^{-4}}{365}$	$\frac{3.65 \times 10^{-4}}{365}$	17
b_W	Transmission rate for water-to-person	ml cells^{-1} day^{-1}	$\frac{3.9 \times 10^{-5}}{365}$	$\frac{2.14 \times 10^{-5}}{365}$	17
t_1	Time of maximum seasonal transmissibility	days	151, May 31	151, May 31	
T	Disease duration	days	300 600 (seasonal)	300 600 (seasonal)	

and the disease related symptomatic death rates are based on the Neilan *et al.* paper.[9]

We assume that the initial size of the population is 100,000. We use the weight parameters, $A = 1, B_1 = 10^{-2}, B_2 = 10$ for our examples. These parameters put the most weight on the infected term in the objective functional; if the costs of

Table 2. Initial conditions used for simulations of cholera transmission.

	Initial conditions	
	Endemic	Introduced
S Susceptible individuals	49,900	100,000
I Infected individuals	100	0
R Recovered individuals	50,000	0
W Pathogens concentration in water (cells ml $^{-1}$)	650	15,000

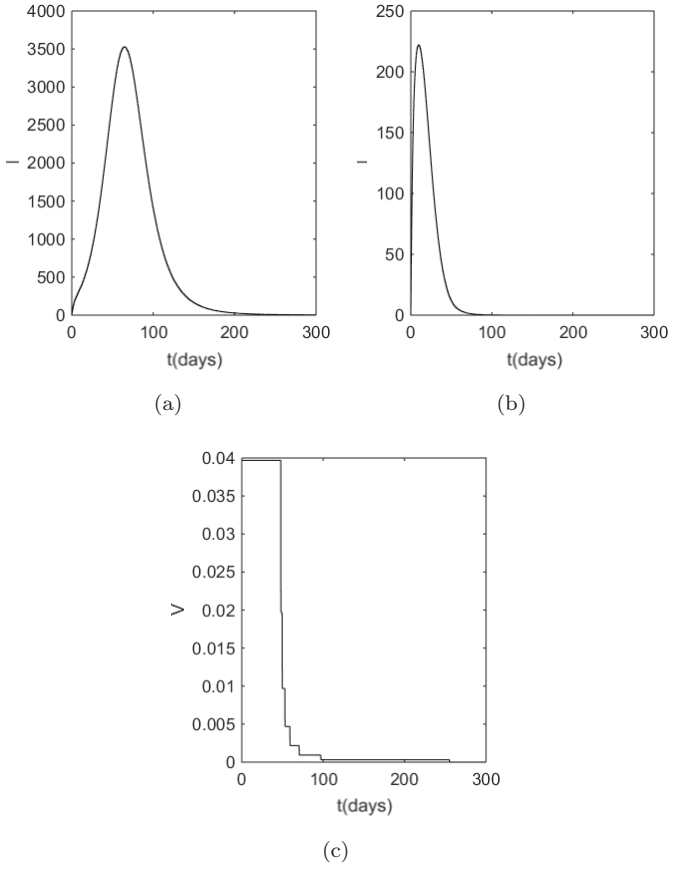


Fig. 1. Introduced case: Comparison between not-controlled and controlled disease dynamics: (a) Disease dynamics without vaccination; (b) Disease dynamics with vaccination; (c) Optimal vaccination strategy.

implementing the vaccination strategies are known to be exceptionally high, then the values of the weight parameters, B_1 and B_2, should be increased.

The numerical simulations are run for two different sets of initial conditions: one with zero infected and recovered populations but with high waterborne pathogen concentration and the other with large recovered population, smaller susceptible population, and relatively low waterborne pathogen concentration. The former represents an introduced case while the latter represents an endemic case (see Table 2).

Figures 1a and 1b suggest vaccination significantly reduces the number of infected individuals. It is crucial to administer vaccination to stop the disease since, without vaccination, the number of infected individuals is as large as 3,500 (Fig. 1a) whereas, it is about 250 with vaccination (Fig. 1b). Furthermore, Fig. 1c indicates vaccination should be administered rigorously for the first couple of months after the first onset of the disease, i.e., with an initial large susceptible population and

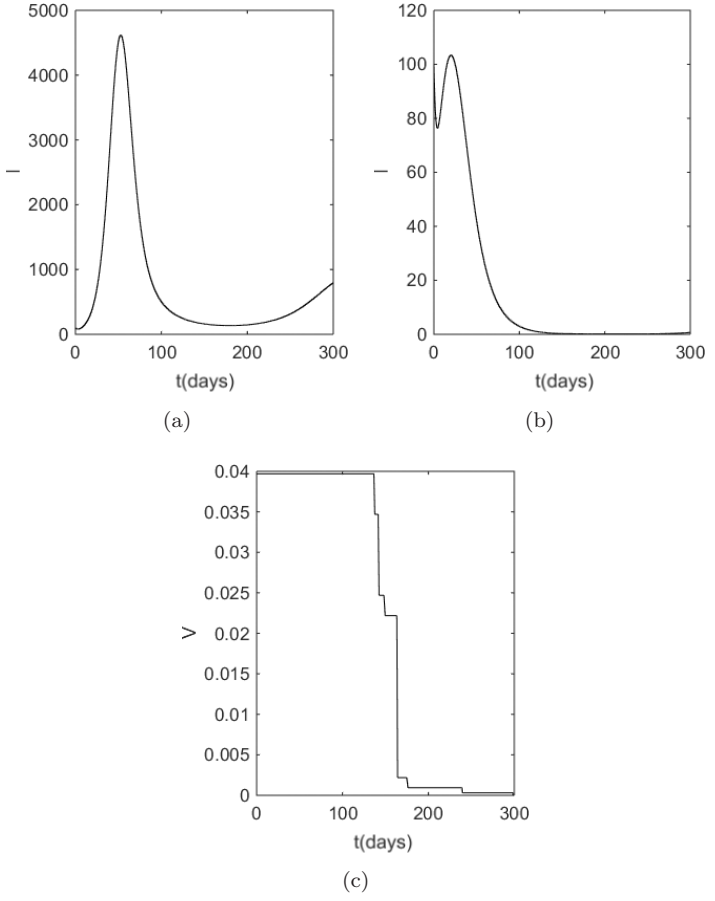


Fig. 2. Endemic case: Comparison between not-controlled and controlled disease dynamics: (a) Disease dynamics without vaccination; (b) Disease dynamics with vaccination; (c) Optimal vaccination strategy.

zero recovered population. Once people move to the recovered class, either due to vaccination or disease recovery, the vaccinations should be stopped gradually within the next 7–8 weeks.

A similar situation is observed for the endemic case (Fig. 2a). A large infected population is observed when no control is used and the disease is endemic, starting with relatively fewer susceptible and a larger number of recovered individuals. Figures 2b and 2c indicate that vaccination effectively controls the infections and that it should be administered at the highest rate for approximately four months. It should then be reduced gradually within the next 14–15 weeks, i.e., for an endemic case, vaccination should be continued at the highest rate for approximately twice as long as that needed for introduced case. Notice also that the second wave of the epidemic appears to be successfully controlled by using the optimal vaccination strategy.

Comparison of disease-related deaths (see Fig. 3) projects significantly a higher number of deaths when no intervention is used. The total number of deaths for the not-controlled introduced, not-controlled endemic, controlled introduced, and controlled endemic cases are, respectively, 29,282, 30,259, 753, and 632. This indicates that when vaccination is administered, approximately 39 and 48 times fewer disease related deaths result for the introduced and endemic cases, respectively.

A similar and comparative study is also performed for seasonal disease dynamics. Seasonality in waterborne pathogen transmission is given by the following function[10]:

$$b_W(t) = B'\left(1 + A'\mathrm{Cos}\left(\frac{2\pi(t - t_1)}{T}\right)\right). \tag{3.1}$$

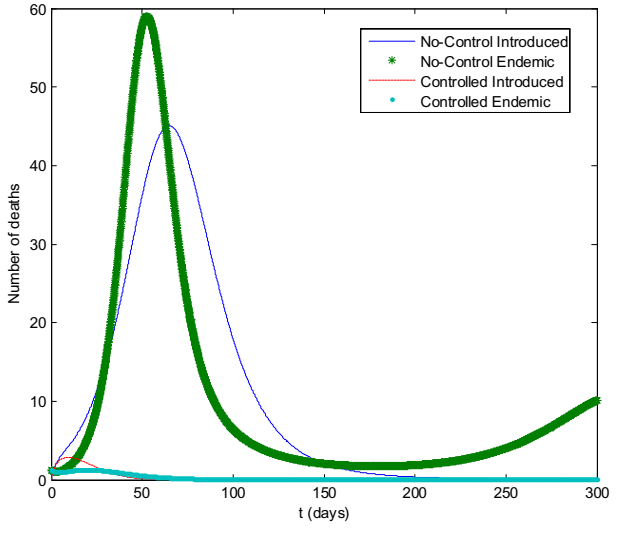


Fig. 3. Comparisons of disease related deaths.

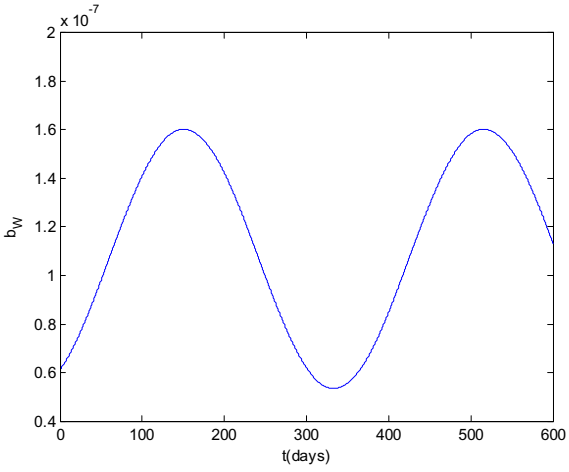


Fig. 4. Seasonality of waterborne pathogen transmission rates.

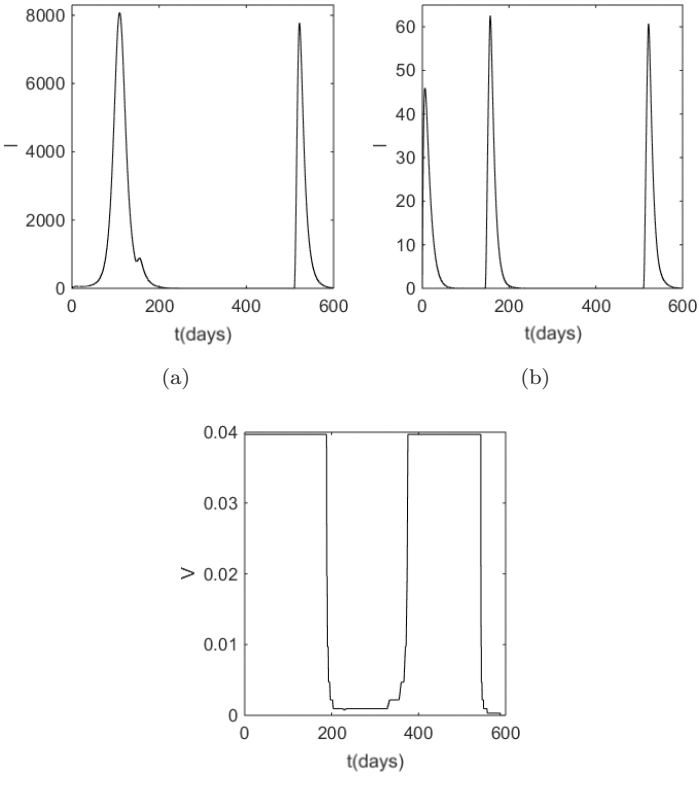


Fig. 5. Introduced case with seasonality: Comparison between not-controlled and controlled disease dynamics: (a) Disease dynamics without vaccination; (b) Disease dynamics with vaccination; (c) Optimal vaccination strategy.

Figure 4 shows seasonal dynamics of waterborne pathogen transmission that peaks during the summer months. Comparisons of Figs. 5a and 5b also suggest that vaccination is a cost-effective way to reduce infection significantly. When no interventions are used, a large number of infected individuals are observed (Fig. 5a). Figure 5c shows that vaccination should be continued at the highest rate for about seven months after the disease has its first onset (introduced case) and should be reduced slowly over the next five months. It should be then increased again during the next seasonal outbreak.

Figures 6a and 6b show comparison between endemic disease dynamics in not-controlled and controlled seasonal disease scenarios. In contrast to the introduced

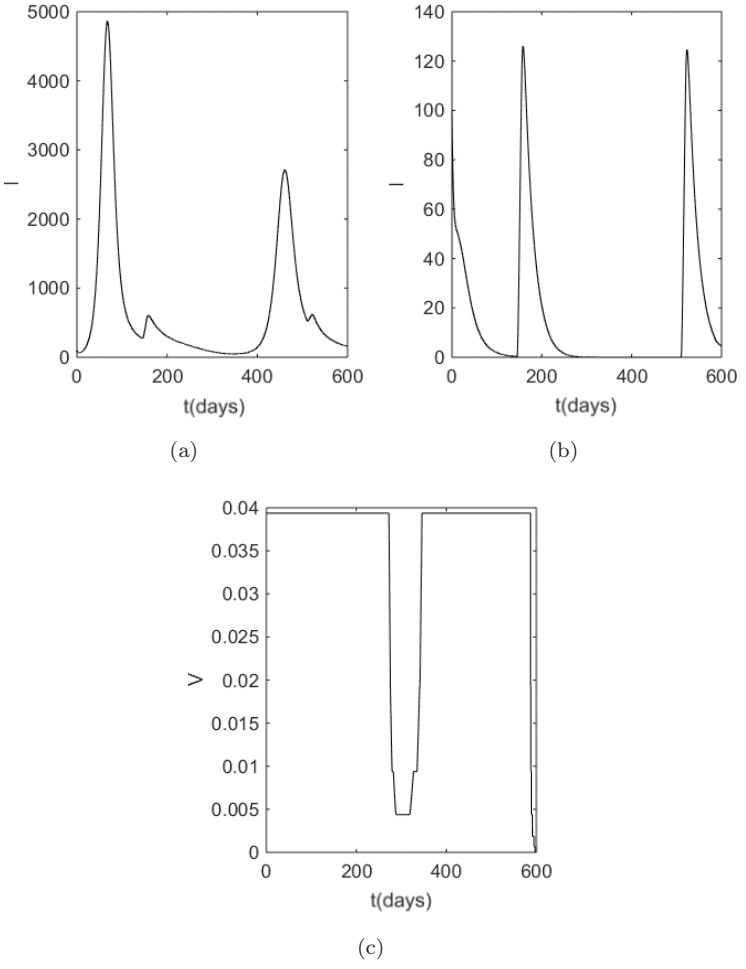
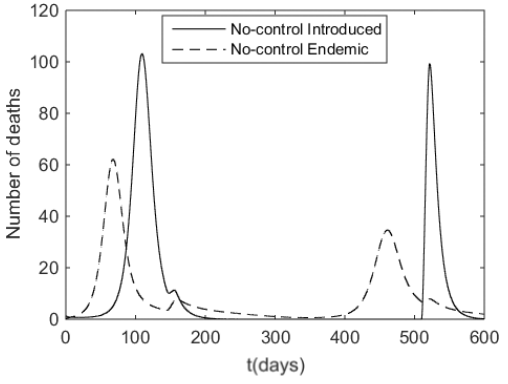


Fig. 6. Endemic case with seasonality: Comparison between not-controlled and controlled disease dynamics: (a) Disease dynamics without vaccination; (b) Disease dynamics with vaccination; (c) Optimal vaccination strategy.

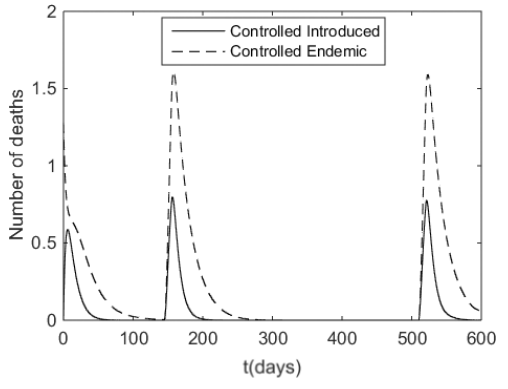
case (Fig. 5c), vaccination should be administered at the highest level for about 10 months when the disease is endemic (Fig. 6c) and then it should be reduced slowly for a brief period of about three weeks before the rates are increased again during the next seasonal outbreak.

Note also, for both introduced and endemic cases, by anticipating the next seasonal outbreak, the optimal strategies suggest an increase rate of vaccination much earlier than the actual disease outbreak. This illustrates the importance of early vaccination (Figs. 5c and 6c).

Figures 7a and 7b show comparisons of seasonal disease-related death dynamics under different scenarios. It is observed that vaccination clearly reduces disease-induced deaths significantly. The total number of deaths over 600 days for not-controlled introduced, not-controlled endemic, controlled introduced, and controlled endemic cases are, respectively, 60,484, 53,585, 410, and 1,294 resulting in 148 (for



(a)



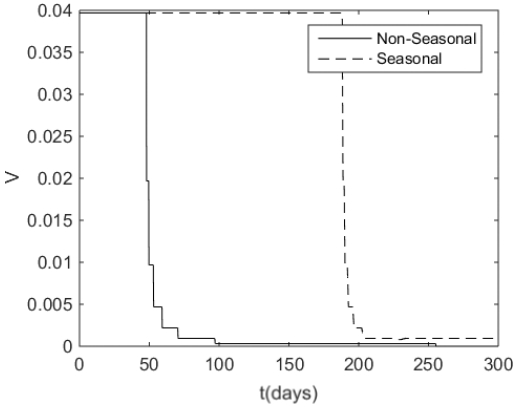
(b)

Fig. 7. Disease induced deaths: Comparisons of disease related deaths for seasonal cases: (a) Without vaccination; (b) With vaccination.

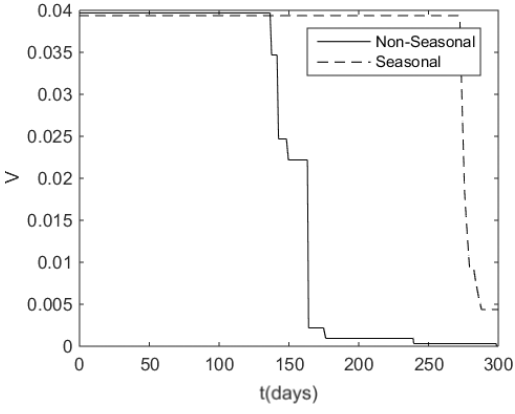
introduced) and 41 (endemic) times fewer disease-related deaths when intervention is used.

Also, comparisons between non-seasonal and seasonal vaccination strategies for both introduced and endemic cases show that vaccination is required at the maximum rate for a much longer time when the disease is seasonal, approximately 3.5 times more than that of the non-seasonal endemic case (see Fig. 8a) and 2.5 times than that for the non-seasonal introduced case (see Fig. 8b). Vaccination should be reduced or stopped when the disease dies out for non-seasonal cases, whereas vaccination should be re-administered at the highest rate once the outbreak recurs for the seasonal cases.

Finally we have studied the optimal vaccination strategies for varying costs i.e., for different values of the weight parameters B_1 and B_2. Analyses indicate different

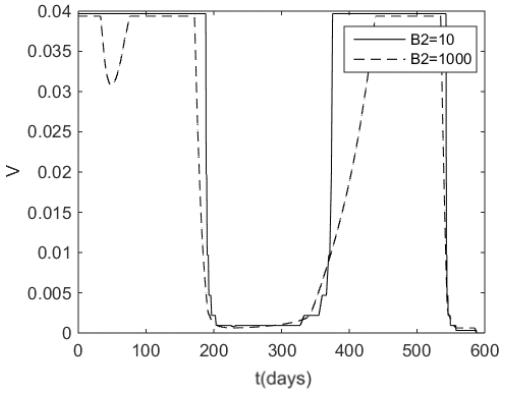


(a)

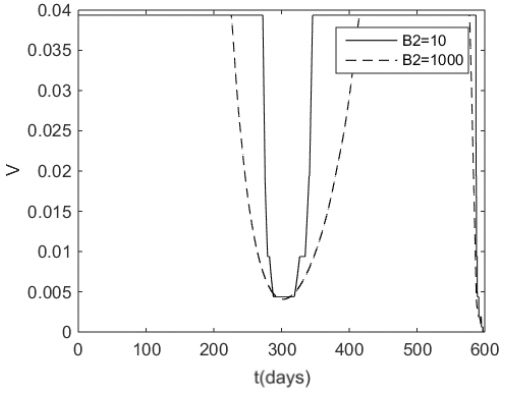


(b)

Fig. 8. Comparison of optimal vaccination strategies: (a) With introduced initial data; (b) With endemic initial data.



(a)



(b)

Fig. 9. Comparison of optimal vaccination strategies for different parameter values: $B_1 = 10^{-2}$, $B_2 = 10$, $B_2 = 1{,}000$: (a) With seasonality and introduced initial data; (b) With seasonality and endemic initial data.
Note: $\frac{A}{B_2} = 0.1$, $\frac{A}{B_2} = 0.001$, $\frac{A}{B_1} = 10^{-2}$ (fixed).

Table 3. Objective functional values obtained from various disease scenarios.

Cases	Objective functional values
Introduced no control	229,260 (300 days)
Introduced controlled	6,804 (300 days)
Endemic no control	236,860 (300 days)
Endemic controlled	5,685 (300 days)
Seasonal, introduced no control	473,550 (600 days)
Seasonal, introduced controlled	4,862 (600 days)
Seasonal, endemic no control	419,510 (600 days)
Seasonal, endemic controlled	11,652 (600 days)

optimal strategies are required for different seasonal disease outbreaks. Vaccination should be reduced earlier for the higher nonlinear cost ($B_2 = 1{,}000$) and increased gradually before the next seasonal outbreak (see Figs. 9a and 9b).

4. Conclusion

In summary, vaccination is a cost-effective strategy for significantly reducing infections and disease-induced deaths. Nielan *et al.* observed that when only vaccination is used, the optimal strategy suggests a high initial rate of vaccination and that there is no "one size fits all" strategy.[9] Similar scenarios are observed here. A non-seasonal endemic case requires the maximum rate of vaccination for approximately twice as long as is needed for non-seasonal introduced cases, whereas a seasonal endemic case requires the highest rate of vaccination of 1.4 times longer duration as is needed for a seasonal introduced case. Results also show that very different optimal vaccination strategies should be used for seasonal and non-seasonal cases. Analyses of all the cases suggest (see Table 3) that vaccination is definitely a cost-effective strategy for disease prevention. Finally, studies with different values of the cost parameters indicate different optimal strategies. In general, if the cost is high, early and gradual reduction of vaccination is possibly the best approach to adopt along with other interventions. Additionally, for higher costs, all seasonal cases suggest gradual and slower increases of vaccination before the next outbreak occurs. Thus, optimal intervention strategies should be decided upon based on different disease scenarios such as seasonal or non-seasonal and initial outbreak conditions. Further work would be needed to extend these results to the case of a constraint on the total number of vaccine doses available (like allocating a fixed vaccine stockpile). In the future, it would also be interesting to consider a more realistic model that would explicitly include the need for two doses of the vaccine.

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