Published in final edited form as:

J Math Biol. 2017 December ; 75(6-7): 1693–1713. doi:10.1007/s00285-017-1133-6.

Optimal control of vaccination rate in an epidemiological model of *Clostridium difficile* transmission

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Abstract

The spore-forming, gram-negative bacteria *Clostridium difficile* can cause severe intestinal illness. A striking increase in the number of cases of *C. difficile* infection (CDI) among hospitals has highlighted the need to better understand how to prevent the spread of CDI. In our paper, we modify and update a compartmental model of nosocomial *C. difficile* transmission to include vaccination. We then apply optimal control theory to determine the time-varying optimal vaccination rate that minimizes a combination of disease prevalence and spread in the hospital population as well as cost, in terms of time and money, associated with vaccination. Various hospital scenarios are considered, such as times of increased antibiotic prescription rate and times of outbreak, to see how such scenarios modify the optimal vaccination rate. By comparing the values of the objective functional with constant vaccination rates to those with time-varying optimal vaccination rates, we illustrate the benefits of time-varying controls.

Keywords

Optimal control; *Clostridium difficile*; vaccination; ordinary differential equations; healthcare setting

1 Introduction

In the United States, one of the most common causes of healthcare associated infections is the spore-forming, toxin-producing bacteria *Clostridium difficile* [18]. Although *C. difficile* was first identified in the 1930s and has since been more intensely studied beginning in the 1970s, there is still difficulty diagnosing, treating, and preventing *C. difficile* infection (CDI) [6]. Between 2000 and 2010, the number of hospitalizations for CDI among adults in the U.S. doubled [18]. This increase coincided with the emergence of the epidemic NAP1/B1/027 strain, which is a highly virulent strain [21]. In 2011, *C. difficile* was estimated to cause approximately 453,000 incident infections and was linked to approximately 29,000

deaths [18]. For acute care facilities alone, the estimated costs associated with *C. difficile* infection are as much as \$4.8 billion [18].

C. difficile spores are commonly found in the environment of healthcare facilities. If ingested, the spores can survive the acidity of the stomach and reach the large intestine, where *C. difficile* can colonize. Typically, the normal gut microbiota prevents *C. difficile* colonization by competing for nutrients and producing inhibitory compounds against *C. difficile*. Antibiotics disrupt the normal gut microbiota, facilitating the colonization of *C. difficile*. Hence, use of antibiotics is the strongest risk factor for developing CDI [16]. Toxins A and B are responsible for most of the clinical manifestations of CDI including diarrhea, abdominal pain, and bloating [16]. Once *C. difficile* reaches large numbers in the colon, both toxins A and B are produced by *C. difficile* [6].

Strategies to control and prevent CDI include antimicrobial usage restriction and stewardship and methods to prevent the patient from exposure to *C. difficile* [5]. Current practice includes identifying patients who have clinical CDI, putting them into isolation, and taking proper contact precautions such as use of gloves, gown, and soap for handwashing [5].

In spite of these current practices, a notable difficulty in studying nosocomial *C. difficile* transmission arises because many colonized patients are asymptomatic. Over the years, there have been discrepancies in determining the relative contributions of asymptomatic carriers versus those of symptomatic patients. In the 1980s, studies were conducted by [3] that concluded symptomatic CDI patients were the main source of *C. difficile* transmission. Therefore, protocol often focused on isolating and taking proper contact precautions with only symptomatic CDI patients. However, since these studies were completed, changes in the epidemiology of *C. difficile* may have altered the relative contributions of symptomatic CDI patients and asymptomatic carriers [14, 30]. Therefore, it is important to identify not only symptomatic patients, but also asymptomatic ones. There are two types of asymptomatic patients: those who are able to mount an immune response and avoid infection and those who are unable to mount an immune response, which leaves them vulnerable to contracting CDI.

Many healthy individuals have antibodies against *C. difficile* toxins A and B, and these antibodies have a protective effect against clinical disease [31]. In a prospective study, patients with low levels of IgG antibodies against toxin A were at greater risk of *C. difficile* diarrhea [12]. Vaccination can be an important addition to the current intervention strategies against *C. difficile*. Currently, several toxoid vaccines (i.e., vaccines that confer immunity against *C. difficile* toxins) are being tested in clinical studies for efficacy, effectiveness, and safety [19]. Toxoid vaccines can provide protection against clinical diseases but not against *C. difficile* colonization. In a simulation study, *C. difficile* vaccination was found to be cost-effective for a range of risk, vaccine efficacies, and vaccine cost in two populations: a target vaccination for patients with CDI undergoing antibiotic treatment and universal vaccination on at-risk patients [15]. Vaccination as an infection control measure was not evaluated. Although vaccination with a toxoid vaccine may not prevent colonization, it may reduce transmission in hospital settings.

In this paper, our goal is to better understand how vaccination would affect the transmission and prevention of CDI in a healthcare setting and also to determine the most cost-effective way to implement a vaccination strategy. In order to accomplish this goal, we use techniques of optimal control on a system of ordinary differential equations (ODEs). See [8, 20, 4, 2, 9, 7, 24] for examples of the use of optimal control theory to design vaccination strategies in ODE models of infectious diseases.

We begin in Section 2 by developing a compartmental model that describes the movement of hospital patients in and out of seven CDI-related states. A control variable representing the vaccination rate is incorporated into the system. Then, in Section 3, we utilize optimal control techniques to determine the time-varying optimal rate at which hospitals should vaccinate in order to minimize the disease prevalence, disease transmission, and the related cost, in terms of both time and money. In Section 4, we discuss the results of our numerical simulations. In particular, we determine optimal vaccination strategies for various hospital statuses, such as times of high transmission of *C. difficile* and periods of increased prescriptions. We also compare the value of the objective functional with a time-varying vaccination rate to that with a constant vaccination rate to determine the benefits of varying the vaccination rate with time. Finally, in Section 5, we discuss our conclusions based on the numerical results.

2 Model

Because mathematical models of disease transmission provide a solid framework for understanding the spread of disease, we begin by extending the mathematical model of *C. difficile* transmission developed by [14] to include vaccination. The original model is a system of ODEs that depicts *C. difficile* transmission within a hospital setting, where all patients are divided into five transition states, measured in number of patients, according to infection status as listed in Table 1.

Resistant patients (R) have not received antimicrobial treatment and have a normal intestinal microbiota [10]. It is assumed that patients with a normal intestinal microbiota are resistant to colonization since patients with a normal flora have a significantly lower risk of developing CDI [14]. Susceptible patients (S) have received antimicrobial treatment and are therefore susceptible to colonization. Colonized patients may or may not mount a protective response. Those who are colonized, asymptomatic, and unable to mount an immune response are labeled C^- and could potentially develop CDI. C^+ patients are also colonized and asymptomatic, but they are able to mount an immune response and do not become diseased. All C^- and C^+ patients are assumed to be colonized during their entire stay at the hospital [23, 27], and both can transmit the disease to the susceptible population. Diseased patients (D) are treated with antibiotics and either become susceptible again or remain infected if treatment is unsuccessful.

In addition to the classes in the original model by [14], we will also consider two additional transition states for vaccinated patients, listed in Table 2. In our model, vaccination will be performed on patients in S , C^- , and C^+ . As previously stated, vaccination does not eliminate colonization from those who are in C^- or C^+ . Because colonized patients, even

asymptomatic ones, contribute to the transmission of disease, it is important to distinguish between those who are vaccinated and those who are vaccinated but also colonized. For this reason, we consider two classes of vaccinated patients. It should also be noted that although C^+ patients are not at risk of contracting CDI, we still vaccinate them because there is not a practical and quick method for distinguishing between C^- and C^+ patients when deciding who needs vaccinating. Therefore, C^+ and C_v^+ have the same infection status, but both of these classes are necessary in the model to keep track of who has been vaccinated and to prevent the same patient from being vaccinated multiple times. Because they have the same infection status, we assume the transmission coefficients for C^+ and C_v^+ are equivalent.

Patients can be discharged and admitted in any of the seven states, but in all cases presented in this paper, we assume that none of the patients are already vaccinated when admitted. All transitions are modeled deterministically as the system of ODEs given in (1), an extension of the model developed by [14]:

$$\begin{aligned}\frac{dR}{dt} &= a_r \delta N + \theta S - (\alpha + k_r) R \\ \frac{dS}{dt} &= a_s \delta N + \alpha R + p\varepsilon D - (\theta + \lambda + k + v) S \\ \frac{dC^-}{dt} &= a_{cn} \delta N + (1-f)\lambda S - (\phi + k + v) C^- \\ \frac{dC^+}{dt} &= a_{cp} \delta N + f\lambda S - (k + v) C^+ \\ \frac{dD}{dt} &= a_d \delta N + \phi C^- - (p\varepsilon + k_d) D \\ \frac{dV}{dt} &= a_v \delta N + v S - (\lambda + k) V \\ \frac{dC_v^+}{dt} &= a_{cv} \delta N + v(C^+ + C^-) + \lambda V - k C_v^+, \quad (1)\end{aligned}$$

where the transmission rate is

$$\lambda = \beta_c (C^- + C^+ + C_v^+) + \beta_d D$$

and

$$N = R + S + C^- + C^+ + D + V + C_v^+.$$

To maintain a constant total population, we define δN similarly to that in [14], which allows discharges to be balanced with admissions:

$$\delta N = k_r R + k S + k C^- + k C^+ + k_d D + k V + k C_v^+. \quad (2)$$

The movement among states described by the system in (1) is illustrated in Figure 1. Details about each parameter are listed in Table 3; a similar table is found in the work completed by [14] with a few modifications and updates made here. Parameter values are based on hospital data or published literature. In particular, the restoration rate of colonization resistance, θ , is taken from [26]. The fraction of colonized patients that mount an immune response, f , comes from [13], and both the treatment rate, ε , and the probability of

successful treatment, p , are taken from [22]. All remaining parameters are either based directly on hospital data or are an adjustment of hospital data to reflect observed disease incidence. More details on these adjustments are given in the following paragraphs.

At the time [14] developed their model, hospital data indicated that the proportion of admitted patients that were asymptotically colonized totaled 2%. Therefore, in [14], $a_{cn} = a_{cp} = 0.01$. Since this time, new research in [1] has indicated that approximately 15% of admitted patients were observed to be asymptotically colonized upon arrival. We divided this updated percentage into 9% admitted with protective response, a_{cp} , and 6% without protective response, a_{cn} . Once these values were determined, the admission proportion for susceptible patients was accordingly decreased by 13% from the value of 22% used in [14], which updated a_s to 0.09 as listed in Table 3. The values for a_v and a_{cv} were assumed to be 0 for all results presented. Once the admission percentages were all adjusted to match updated observed rates, the transmission coefficients, β_c and β_d , and the clinical disease rate, ϕ , were then adjusted so that the average number of observed incident cases of CDI per month per ward was comparable to the value of 2.2 given in [14].

We define the vaccination rate v to be the *effective* vaccination rate, which encompasses both effort and efficacy. To estimate a feasible range of values for the effective vaccination rate v , we solved the system in (1) numerically for various v values and noted the resulting percentage of patients who were effectively vaccinated out of the total number of patients admitted over a 30-day period. A few of these scenarios are summarized in Table 4. While determining this range for the vaccination rate, we decided for most simulations to not consider cases in which significantly more than 50% of those admitted in 30 days were effectively vaccinated. Therefore, we concentrate most of our focus on $0 \leq v \leq 0.3$. Because of the short time frame evaluated, we do not consider waning immunity.

In this paper, we assume a hospital setting containing five wards of 30 beds each for a total population of $N = 150$ patients, which is kept constant by assumption (2). The initial conditions used were based on the admission proportions given in the list of parameter values shown in Table 3; that is, we set $R(0) = 112$, $S(0) = 14$, $C^-(0) = 9$, $C^+(0) = 13$, $D(0) = 2$, $V(0) = 0$, and $C_v^+(0) = 0$.

3 Optimal control of vaccination rate

We implement optimal control on the vaccination rate v to determine the time-varying, optimal rate of vaccination over a particular time period because the cost-effectiveness of a vaccine, in terms of both monetary and time resources, is so important. Our goal is to minimize not only the overall impact of the disease but also the cost associated with vaccination over a given period of time, $[0, T]$ for $T > 0$. The objective functional that represents this goal is shown in (3).

$$J(v) := c_0 C^-(T) + \int_0^T \left[c_1 v(t) \left(S(t) + C^-(t) + C^+(t) \right) + c_2 (v(t))^2 + c_3 D(t) + c_4 C^-(t) + c_5 \lambda(t) (S(t) + V(t)) \right] dt$$

(3)

The first term in the objective functional, $c_0 C^-(T)$, counts the number of patients asymptotically colonized without protection at the final time and also ensures that the value of the control is not forced to zero for some $t \in [0, T]$, as further explained in Section 4.1. The next term, $c_1 v(t) (S(t) + C^-(t) + C^+(t))$, represents the linear cost associated with the vaccination process while $c_2 (v(t))^2$ represents the nonlinear cost that arises from difficulties faced when implementing a successful vaccination program. The objective functional also accounts for the number of diseased patients with the term $c_3 D(t)$; by including this term, the disease prevalence in the population will be minimized. Additionally, the objective functional includes terms for the number of C^- patients, $c_4 C^-(t)$, and for nosocomial disease transmission, $c_5 \lambda(t) (S(t) + V(t))$. Recall the transmission rate

$\lambda(t) = \beta_c (C^-(t) + C^+(t) + C_v^+(t)) + \beta_d D(t)$. The coefficients c_i , $0 \leq i \leq 5$, represent weights on the different terms of the objective functional. For some $M > 0$, the control set is

$$V^* := \{v: [0, T] \rightarrow [0, M] : v \text{ Lebesgue measurable}\}.$$

The goal is to characterize the optimal control v^* satisfying

$$\inf_{v \in V^*} J(v) = J(v^*),$$

subject to the state system (1) with specified nonnegative initial conditions for R , S , C^- , C^+ , D , V , and C_v^+ .

3.1 Existence of optimal control

In order to use Pontryagin's Maximum Principle [25] to characterize an optimal control, we must first prove that an optimal control exists. See [11] for an argument similar to the one presented here.

Theorem 1—*There exists an optimal control v^* that minimizes the objective functional $J(v)$ in (3).*

Overview of proof: The structure of the state system (1) together with nonnegative initial conditions implies that each state function is nonnegative [28, 29]. Since we assume a constant total population, the states are uniformly bounded above.

Because our objective functional is bounded below, there exists a minimizing sequence of controls, $\{v_n\}$. Let $\{R_n\}$, $\{S_n\}$, $\{C_n^-\}$, $\{C_n^+\}$, $\{D_n\}$, $\{V_n\}$, and $\{(C_v^+)_n\}$ be the corresponding state sequences. From the structure of the state system, uniform bounds on the controls and states give uniform bounds on the derivatives of the states, which implies equicontinuity of the states. Thus on a subsequence, the states converge uniformly, and the controls converge weakly in $L^2(0, T)$ to v^* . Passing to the limit in the state system on the subsequence gives the limits of the state sequences as the states corresponding to the control v^* . Using lower semi-continuity of the L^2 -norm with respect to weak convergence in passing to the limit in $J(v_n)$, we obtain that v^* is an optimal control.

3.2 Characterization of optimal control

Now that we have established existence, we can apply Pontryagin's Maximum Principle [25] to derive necessary conditions on the optimal control.

Theorem 2—Given an optimal control v^* and solutions to the corresponding state system in (1), there exist adjoint variables λ_i , $i = 1, \dots, 7$, satisfying

$$\begin{aligned}
 \lambda_1' &= -\lambda_1(a_r k_r - \alpha - k_r) - \lambda_2(a_s k_r + \alpha) - k_r(\lambda_3 a_{cn} + \lambda_4 a_{cp} + \lambda_5 a_d) \\
 &\quad - k_r(\lambda_6 a_v + \lambda_7 a_{cv}) \\
 \lambda_2' &= -c_1 v - c_5 \lambda - \lambda_1(k a_r + \theta) - \lambda_2(a_s k - \theta - k - \lambda - v) \\
 &\quad - \lambda_3[a_{cn} k + (1-f)\lambda] - \lambda_4(a_{cp} k + f\lambda) - \lambda_5 a_d k \\
 &\quad - \lambda_6(k a_v + v) - \lambda_7 a_{cv} k \\
 \lambda_3' &= -c_1 v - c_4 - c_5 \beta_c(S+V) - \lambda_1 a_r k - \lambda_2(k a_s - \beta_c S) \\
 &\quad - \lambda_3[a_{cn} k + (1-f)\beta_c S - \phi - k - v] - \lambda_4(f\beta_c S + k a_{cp}) \\
 &\quad - \lambda_5(k a_d + \phi) - \lambda_6(k a_v - \beta_c V) - \lambda_7(\beta_c V + k a_{cv} + v) \\
 \lambda_4' &= c_1 v - c_5 \beta_c(S+V) - \lambda_1 a_r k - \lambda_2(k a_s - \beta_c S) - \lambda_3[a_{cn} k + (1-f)\beta_c S] \\
 &\quad - \lambda_4(f\beta_c S + k a_{cp} - k - v) - \lambda_5 a_d k - \lambda_6(k a_v - \beta_c V) \\
 &\quad - \lambda_7(\beta_c V + k a_{cv} + v) \\
 \lambda_5' &= -c_3 - c_5 \beta_d(S+V) - \lambda_1 a_r k_d - \lambda_2(p\varepsilon - \beta_d S + a_s k_d) \\
 &\quad - \lambda_3[a_{cn} k_d + (1-f)\beta_d S] - \lambda_4(f\beta_d S + a_{cp} k_d) - \lambda_5(a_d k_d - p\varepsilon - k_d) \\
 &\quad - \lambda_6(a_v k_d - \beta_d V) - \lambda_7(\beta_d V + a_{cv} k_d) \\
 \lambda_6' &= -c_5 \lambda - \lambda_1 a_r k - \lambda_2 k a_s - \lambda_3 a_{cn} k - \lambda_4 a_{cp} k - \lambda_5 a_d k \\
 &\quad - \lambda_6(a_v k - k - \lambda) - \lambda_7(a_{cv} k + \lambda) \\
 \lambda_7' &= -c_5 \beta_c(S+V) - \lambda_1 a_r k - \lambda_2(k a_s - \beta_c S) - \lambda_3[a_{cn} k + (1-f)\beta_c S] \\
 &\quad - \lambda_4(f\beta_c S + k a_{cp}) - \lambda_5 a_d k - \lambda_6(k a_v - \beta_c V) - \lambda_7(\beta_c V + k a_{cv} - k), \\
 \lambda_i(T) &= 0, \quad \text{for } i \neq 3 \\
 \lambda_3(T) &= c_0.
 \end{aligned} \tag{4}$$

Furthermore, v^* is represented as

$$v^* = \min\{M, \max\{0, \hat{v}\}\}, \tag{5}$$

where

$$\hat{v} = \frac{\lambda_2 S + \lambda_3 C^- + \lambda_4 C^+ - \lambda_6 S - \lambda_7 (C^+ + C^-) - c_1 (S + C^+ + C^-)}{2c_2}. \quad (6)$$

Proof—The Hamiltonian is given by

$$H = c_1 v (S + C^- + C^+) + c_2 v^2 + c_3 D + c_4 C^- + c_5 (S + V) \lambda \\ + \lambda_1 \frac{dR}{dt} + \lambda_2 \frac{dS}{dt} + \lambda_3 \frac{dC^-}{dt} + \lambda_4 \frac{dC^+}{dt} + \lambda_5 \frac{dD}{dt} + \lambda_6 \frac{dV}{dt} + \lambda_7 \frac{dC_v^+}{dt}.$$

Pontryagin's Maximum Principle [25] gives the existence of adjoint variables satisfying the system in (4) using

$$\lambda'_1 = -\frac{\partial H}{\partial R}, \quad \lambda'_2 = -\frac{\partial H}{\partial S}, \quad \lambda'_3 = -\frac{\partial H}{\partial C^-}, \quad \lambda'_4 = -\frac{\partial H}{\partial C^+}, \quad \lambda'_5 = -\frac{\partial H}{\partial D}, \\ \lambda'_6 = -\frac{\partial H}{\partial V}, \quad \text{and} \quad \lambda'_7 = -\frac{\partial H}{\partial C_v^+},$$

with transversality conditions $\lambda_i(T) = 0$ for $i = 3$ and $\lambda_3(T) = c_0$. We then have

$$\frac{\partial H}{\partial v} = c_1 (S + C^- + C^+) + 2c_2 v - \lambda_2 S - \lambda_3 C^- - \lambda_4 C^+ + \lambda_6 S + \lambda_7 (C^- + C^+).$$

On the interior of the control set, $\frac{\partial H}{\partial v}|_{v^*} = 0$. Thus, we can solve for the optimal control on the interior:

$$v^*(t) = \frac{\lambda_2 S + \lambda_3 C^- + \lambda_4 C^+ - \lambda_6 S - \lambda_7 (C^- + C^+) - c_1 (S + C^- + C^+)}{2c_2}.$$

Note that on $\{t|v^* = 0\}$, $\frac{\partial H}{\partial v} \geq 0$ and on $\{t|v^*(t) = M\}$, $\frac{\partial H}{\partial v} \leq 0$. Combining all three cases leads to the characterization of our optimal control given in (5).

4 Numerical results

The optimality system, which consists of the state system in (1) with initial conditions, adjoint system in (4) with transversality conditions, and characterization of the optimal control in (5), is solved using a Forward-Backward Sweep method [17]. This is an iterative method that solves the system using a fourth-order Runge-Kutta (RK4) scheme. We start with an initial guess for our control value and then use RK4 and the given initial conditions to solve the state system in (1) forward in time. Then, we use the initial control guess, the transversality conditions given for our adjoints, and the values for the state system solution to solve the adjoint system in (4) backward in time. Next, our control value v is updated by entering the new state and adjoint values into the characterization of the control in (5).

Finally, convergence is checked, and the process is repeated until values converge sufficiently.

Unless otherwise stated, $M = 0.3$ per day so that $0 \leq v(t) \leq 0.3$ as discussed at the end of Section 2. Additionally, we set $T = 30$ so that we are considering 30-day intervals. Short periods of time are considered because the hospital will change states, thereby potentially shifting some parameter values, and the vaccination strategy will need to be reevaluated after the 30 days and possibly modified in response to this shift.

4.1 Summary of exploration into weighting coefficient values

Before any results were determined, we first gained an understanding of how changing the values of our weighting coefficients, c_i , affected the optimal control, v^* . Because vaccination against CDI is still in testing, we do not have data that details the cost associated with such a program. Once this data is known, it can be incorporated into the appropriate weighting coefficient values. For now, to establish how a particular weighting coefficient changes the optimal vaccination rate, we varied the value for one weighting coefficient while keeping all other coefficients fixed, some at 0. Additionally, we compared the relative size of each term, without being multiplied by the corresponding weighting coefficient, in the objective functional $J(v)$ given in (3). In particular, we observed that the nonlinear cost associated with vaccination, given as v^2 , and the transmission, $\lambda(S + V)$, are relatively small in comparison to the other terms. Therefore, we allow their corresponding weighting coefficients, c_2 and c_5 , to be relatively large in comparison to the remaining coefficients.

After considering various scenarios in which we varied one weighting coefficient value while keeping the others fixed, we made several conclusions. First, we concluded that if control cost coefficient c_1 exceeds some threshold value, then $v^*(t) = 0$ for all $t \in [0, T]$. Since we do not want to consider a case in which vaccination is too costly to implement at all, we keep c_1 relatively small. Note that because the nonlinear cost term is smaller than the linear cost term in the objective functional, increasing c_2 does not force v^* to be 0 for the entire time period in the way that increasing c_1 does.

Next, note that if c_0 , the weighting coefficient on the final time condition, is 0, the optimal vaccination rate will always drop down to 0 at some point in our time period no matter what the values are for the remaining weighting coefficients. In fact, there exists some threshold value $\hat{c}_0$ such that for $c_0 < \hat{c}_0$, $v^*(t) = 0$ for $t \in [\hat{t}, T]$, for some $\hat{t} \in [0, T]$. This is because if $c_0 = 0$, then $\lambda_f(T) = 0$ for $i = 1, \dots, 7$, which means $\hat{v}$, in (6), is negative at the final time, and by the characterization of the optimal control in (5), this implies $v^*(T) = 0$. It is not practical to have to drop down to a vaccination rate of 0 in every scenario; therefore, we considered values for c_0 large enough to prevent this forced decrease to 0. Finally, note that an increase in c_3 or c_4 adds emphasis to our desire to minimize the overall impact of the disease and thereby leads to an increased v^* . The last term in $J(v)$, $c_5 \lambda(S + V)$, involves a bit of a balancing act. We want to increase the number of vaccinated patients V while also minimizing this term as part of the objective functional. Thus, depending on the value of V , increasing c_5 may decrease v^* or increase v^* .

The exploration of values summarized in this section provided us with an idea of how to set weighting coefficient values in the simulations to come. The weighting coefficient values chosen are as follows: $c_0 = 3$, $c_1 = 0.1$, $c_2 = c_5 = 15$, and $c_3 = c_4 = 0.5$, and the resulting v^* obtained using this combination of weighting coefficients is shown in Figure 2.

4.2 Determining the impact of vaccination

In this section, we compare the population behavior with no vaccination to its behavior with vaccination implemented using optimal control and observe the differences. In Figure 3, the optimal states that correspond to the time-varying optimal vaccination rate v^* illustrated in Figure 2 are plotted alongside the states corresponding to no vaccination. We see from Figure 3 that without vaccination, each of the classes reaches its steady state before the 30 days have expired. Furthermore, Figure 3 illustrates that this particular vaccination rate v^* decreases the number of patients in C^- by approximately 4 in 30 days and the number of patients in D by approximately 2. Figure 3 also shows that the total number of colonized patients remains approximately the same (a difference of less than 1 person) when this optimal time-varying vaccination rate is implemented. Additionally, vaccination also leaves the hospital with a significantly lower number of patients who are susceptible to becoming colonized (approximately 47 fewer), which is significant since *C. difficile* spores can survive for extended time periods on various hospital surfaces.

Because the restriction of $M = 0.3$ per day is not a strict one, we also considered an increased upper bound on v . Figures 4(a) and 4(b) compare the optimal vaccination rate v^* for $M = 0.3$ per day to that in the increased case of $M = 0.6$ per day with the same weighting coefficient values previously considered. Observe from Figure 4(a) that for this case, an increase in M only initially alters v^* . Figure 4(b) zooms in on this initial change in v^* by displaying an interval of only 3 days. Additionally, note that the v^* obtained for $M = 0.6$ produces the exact same corresponding state populations for all 30 days that the v^* with $M = 0.3$ produces (results not shown).

To determine the impact of using a time-varying vaccination rate, we compare the value of the objective functional, $J(v)$ in (3), obtained with our time-varying optimal vaccination rate to that obtained with a constant vaccination rate of 0.3 per day for the entire time period. For the particular case of weighting coefficient values illustrated in Figures 2 and 3 and for the case with an increased upper bound (shown in Figure 4), various $J(v)$ values are compared in Table 5. First, observe that whether $M = 0.3$ or $M = 0.6$, a time-varying optimal vaccination rate engenders a savings over a constant rate. Furthermore, if M is increased to 0.6 per day, then a time-varying vaccination rate leads to a much more notable savings over the case of a constant rate than the $M = 0.3$ case does. Thus, if we allow for an increased upper bound on the vaccination rate, then we see a more stark difference and impact of time-varying vaccination versus that of constant vaccination.

4.3 An increase in susceptible patients

In this section, we explore the question of how hospitals should modify their vaccination strategy in order to handle a larger number of susceptible patients. To do this, we consider

alternate hospital statuses in which an increased number of patients have either received antibiotics after admission or taken them prior to admission.

First, if a particular hospital is prescribing high-risk antibiotics at an increased rate, this corresponds to an increase in α and thereby also an increase in the number of susceptible patients since more patients will have an altered intestinal microbiota. For all simulations thus far, $\alpha = 0.5$ per day as listed in Table 3. Figure 5 illustrates how v^* changes for increasing α . Note that as α is increased, v^* decreases. To understand this downward shift, we first compare the patient population dynamics for the various α values, shown in Figure 6. From this, we see that when α is increased, we are able to reduce C^- and D to approximately the same number seen for the lower α -value of 0.5, but we do so with a lower v^* and therefore also a lower value of J . Additionally, with the higher antibiotic prescription rate, we observe that the total colonized population is also decreased.

Note that the number of susceptible patients vaccinated per day is given by vS . Since S is increased in this scenario, v^* can correspondingly decrease to lead to the same, or even a slightly increased, number of susceptible patients being vaccinated per day. Essentially, because there is an increased number of susceptible patients available to vaccinate due to the increase in α , we are able to vaccinate more patients (even at a lower rate). This increase in V engenders the decrease in the number of C^- and D patients. From Table 6, observe that we vaccinate more patients as α is increased whether we use a constant vaccination rate or a time-varying one. Furthermore, Table 6 also indicates that time-varying rates of vaccination in this scenario may be more economical than constant rates.

Another way for a hospital to experience an increase in susceptible patients is to have more upon admission due to a greater number of patients taking antibiotics before entering the hospital. We considered this case by increasing the proportion of susceptible patients admitted, a_s , and thereby also increasing the initial number of susceptible patients by adjusting the remaining admission proportions and initial conditions to reflect the change. This scenario produced results that were similar to those obtained when increasing α and are omitted here.

4.4 Increasing transmission coefficients

Another scenario we considered is the case of an outbreak, meaning an increase in the transmission coefficients, β_c and β_d . Such an increase in transmission coefficients could occur for a multitude of reasons, one of which being an understaffed hospital in which workers may not be following proper protocol such as adequate washing of hands and wearing of gloves when necessary. Additionally, note that the system in [14] was found to be particularly sensitive to β_c , so we determined the case of changing β_c was one worth exploring. Recall that thus far $\beta_c = \beta_d = 10^{-6}$.

Figure 7 shows how such an increase in β_c and β_d affects the optimal vaccination rate. As expected, in such a scenario, we should increase the vaccination rate in order to contain the outbreak. As β_c and β_d are increased, a time-varying optimal vaccination rate is just barely more cost-effective than a constant vaccination rate since v^* is increased closer to its maximum allowed rate of 0.3 per day. The savings in $J(v)$ are decreased as β_c and β_d are

increased, as shown in Table 7. In a particularly bad outbreak, the optimal vaccination rate is constant at the upper bound of $M = 0.3$, as shown in Figure 7 for $\beta_c\beta_d = 0.007$.

The resulting patient state dynamics for each set of transmission coefficient values considered in Figure 7 are illustrated in Figure 8. For the increased transmission coefficient values of $\beta_c\beta_d = 0.007$, a comparison of the state dynamics with no vaccination to those with vaccination implemented using optimal control is shown in Figure 9. In this case, observe that vaccination has a much more significant impact than the scenario shown in Figure 2, and in 30 days decreases the number of C^- patients by approximately 20 and the number of D patients by approximately 10.

We also considered scenarios in which we increased the clinical disease rate ϕ while simultaneously increasing the transmission coefficients β_c and β_d . Note that in this case, the trend remains essentially the same to that when only β_c and β_d are increased. The only difference is that there is an increase in D when ϕ is also increased, which is expected. Because the results were similar, they are omitted.

Note that an increase in the upper bound M on the vaccination rate may be reasonable for some hospitals depending on a combination of factors. One such factor is how many people a hospital can manage to vaccinate in a day. If staff increases its efforts, the hospital may be able to handle an increase in vaccination rate. Additionally, if it becomes easier to convince persons to be vaccinated, such a scenario would also call for an increase in M . Since the most extreme outbreak, with $\beta_c\beta_d = 0.007$, forces v^* to become constant at its upper bound, we also wanted to explore how v^* would change with an increase in the upper bound M to 0.6. The resulting v^* is illustrated in Figure 10 alongside v^* with $M = 0.3$. The corresponding state trajectories are given in Figure 11 for $M = 0.3$ and 0.6. This figure shows that D and C^- are decreased more in the case when $M = 0.6$ than when $M = 0.3$. Furthermore, from Table 8, observe that in the case of the increased upper bound, there is a notable benefit to using time-varying control over a constant rate of vaccination for all 30 days. Notably, the value of $J(v)$ for the optimal v^* corresponding to $M = 0.6$ is smaller than the value of $J(v)$ for the optimal v^* corresponding to $M = 0.3$. Thus, allowing for an increase in the upper bound on $v(t)$ could lead to an overall savings and a greater impact on reducing disease prevalence and incidence. We conclude that time-varying vaccination could be beneficial in more extreme outbreak scenarios (i.e., $\beta_c\beta_d = 0.007$) with this upper bound increase, whereas without this increase, a constant rate of vaccination would be preferred.

5 Discussion

The recent striking growth in the prevalence of *Clostridium difficile* infection (CDI) in healthcare facilities highlights the need for finding effective strategies for prevention. A new potential prevention strategy is being considered as two international studies are underway to test the effectiveness of a vaccine against the toxins produced by *C. difficile* [16]. In anticipation of this vaccine, we have extended and updated a mathematical model of *C. difficile* transmission in hospitals to include vaccination. We then employed optimal control theory in order to find the time-varying optimal rate at which hospitals should vaccinate

patients that minimizes disease prevalence and transmission while also minimizing the cost associated with vaccination.

In this paper, our simulations considered 30-day time periods since vaccination strategies will need to be reevaluated after this due to parameter values that may change during this period. We considered different hospital statuses and compared time-varying rates to constant rates in order to determine in which scenarios a time-varying rate would be preferred. First, we considered a scenario in which hospitals have an increased number of susceptible patients due to more high-risk antibiotics being given either prior to or after admission. We saw that with this increase in the number of susceptible patients, the optimal vaccination rate decreased. In this scenario, hospitals could reduce all colonized populations (asymptomatic and symptomatic) by the same amount (or slightly more), with a lower vaccination rate and lower objective functional value. This is because there are more patients available to be vaccinated in this scenario. In this case, a time-varying rate of vaccination was shown to be more beneficial.

Another situation that hospitals commonly experience is that of an outbreak. In this scenario, we saw that an increase in transmission coefficients led to a simultaneous increase in the optimal vaccination rate. Because part of our main goal is to minimize disease prevalence and transmission, as *C. difficile* spores are being transmitted at a higher rate, we must vaccinate more to control this outbreak. Once the transmission coefficients increased to some threshold value, the optimal vaccination rate became constant at its upper bound. Therefore, in more severe outbreaks a constant vaccination rate is optimal to accomplish our goal rather than a time-varying one, unless we allow for an increase in the upper bound on the vaccination rate.

It is important to note that the upper bound of 0.3 we imposed on the vaccination rate is not a strict upper bound. For this reason, we also considered how an increased upper bound changed our results. In particular, we observed that in some cases of severe outbreak a time-varying optimal vaccination rate is more economical when the upper bound is increased.

The results we obtained in this paper are only a starting point for the analysis of vaccination against CDI. Because such a vaccine is still in testing, we were unable to incorporate data for quantities such as the monetary cost associated with this vaccination program. Once this data is obtained, a more quantitative modeling study could be carried out.

Acknowledgments

This work was supported by the joint DMS/NIGMS Mathematical Biology Program through NIH award #R01GM113239.

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Fig. 1.
Summary of movement among patient transition states with corresponding parameters

Fig. 2.

Optimal vaccination rate v^* for $c_0 = 3$, $c_1 = 0.1$, $c_2 = c_5 = 15$, $c_3 = c_4 = 0.5$, $M = 0.3$, and $T = 30$

Fig. 3.

Dynamics of patient transition states with optimal vaccination rate v^* shown in Figure 2 compared to those without vaccination for $c_0 = 3$, $c_1 = 0.1$, $c_2 = c_5 = 15$, $c_3 = c_4 = 0.5$, $M = 0.3$, and $T = 30$

Fig. 4.

(a) Comparison of optimal vaccination rate v^* with upper bound $M=0.3$ to that with the increased value of $M=0.6$ with $c_0=3$, $c_1=0.1$, $c_2=c_5=15$, $c_3=c_4=0.5$, and $T=30$ (b) View of (a) over a 3-day interval to observe the initial difference in v^*

Fig. 5.

Optimal vaccination rate v^* for increasing antibiotic prescription rate, α , and for $c_0 = 3$, $c_1 = 0.1$, $c_2 = c_5 = 15$, $c_3 = c_4 = 0.5$, $M = 0.3$, and $T = 30$

Fig. 6.

Dynamics of patient transition states for increasing antibiotic prescription rate, α , and for $c_0 = 3$, $c_1 = 0.1$, $c_2 = c_5 = 15$, $c_3 = c_4 = 0.5$, $M = 0.3$, and $T = 30$

Fig. 7.

Optimal vaccination rate v^* for increasing transmission coefficients, β_c, β_d and for $c_0 = 3$, $c_1 = 0.1$, $c_2 = c_5 = 15$, $c_3 = c_4 = 0.5$, $M = 0.3$, and $T = 30$

Fig. 8. Dynamics of patient transition states for increasing transmission coefficients, β_c, β_d and for $c_0 = 3$, $c_1 = 0.1$, $c_2 = c_5 = 15$, $c_3 = c_4 = 0.5$, $M = 0.3$, and $T = 30$

Fig. 9.

Dynamics of patient transition states with vaccination rate shown in Figure 7 for the increased values of $\beta_c\beta_d = 0.007$ compared to those without vaccination for $c_0 = 3$, $c_1 = 0.1$, $c_2 = c_5 = 15$, $c_3 = c_4 = 0.5$, $M = 0.3$, and $T = 30$

Fig. 10.

Optimal vaccination rate v^* for increasing M with increased $\beta_c\beta_d=0.007$, $c_0=3$, $c_1=0.1$, $c_2=c_5=15$, $c_3=c_4=0.5$, and $T=30$

Fig. 11.

Dynamics of patient transition states with optimal vaccination rates shown in Figure 10 with various upper bounds M for the increased values of $\beta_c, \beta_d = 0.007$ for $\alpha_0 = 3$, $c_1 = 0.1$, $c_2 = c_5 = 15$, $c_3 = c_4 = 0.5$, $M = 0.3$, and $T = 30$

Table 1

Patient transition states developed in [14]

State	Infection status
R	resistant to colonization
S	susceptible to colonization
C^-	asymptotically colonized without protection against CDI
C^+	asymptotically colonized with protection against CDI
D	diseased (with CDI)

Table 2

Additional patient transition states for vaccinated patients

State	Infection status
V	vaccinated for CDI and not colonized
C_v^+	asymptotically colonized and vaccinated

Table 3

Model parameter descriptions and values

Symbol	Description, units	Baseline Value
a_r	Proportion of admitted patients that are resistant, dimensionless	0.75
a_s	Proportion of admitted patients that are susceptible, dimensionless	0.09
a_{cn}	Proportion of admitted patients that are colonized without protective response, dimensionless	0.06
a_{cp}	Proportion of admitted patients that are colonized with protective response, dimensionless	0.09
a_d	Proportion of admitted patients with <i>C. difficile</i> infection, dimensionless	0.01
a_v, a_{cv}	Proportion of admitted patients who are vaccinated and vaccinated who are colonized, respectively, dimensionless	0
α	Antibiotic prescription rate, per day	0.5
θ	Restoration rate of colonization resistance, per day	0.033
β_c, β_d	Transmission coefficients for asymptomatic carriers and diseased patients, respectively, per individual-day	10^{-6}
f	Fraction of colonized patients that mount immune response, dimensionless	0.6
e	Treatment rate, per day	0.1
p	Probability of successful treatment, dimensionless	0.8
ϕ	Clinical disease rate, per day	0.06
k_r	Discharge rate for resistant patients, per day	0.33
k	Discharge rate for susceptible, colonized, and vaccinated patients, per day	0.15
k_d	Discharge rate for diseased patients, per day	0.068
v	Vaccination rate, per day	varied

Table 4

Exploration of a biologically feasible range of values for vaccination rate, v

v	% effectively vaccinated out of total admitted (in 30 days)
2	73.46%
1	67.51%
0.5	58.07%
0.3	48.91%
0.1	27.24 %
0.05	16.33%

Table 5

Comparison of $J(v)$ with constant vaccination rate to $J(v)$ with time-varying optimal vaccination rate, shown in Figure 4, for various upper bounds, M , on $v(t)$

M	$J(v)$ with constant $v(t) = M$	$J(v)$ with time-varying optimal v^*
0.3	203	192
0.6	305	192

Table 6

Comparison of $J(v)$ and total vaccinated with constant vaccination rate to $J(v)$ and total vaccinated with time-varying optimal vaccination rate, shown in Figure 5, for various antibiotic prescription rates, α

α	$J(v)$ with Constant $v(t) = 0.3$	$J(v)$ with Time-varying Optimal v^*	Total Vaccinated With constant $v(t) = 0.3$	Total vaccinated With Time-varying Optimal v^*
0.5	203	192	405	319
1	201	187	447	332
5	199	181	493	338

Table 7

Comparison of $J(v)$ with constant vaccination rate to $J(v)$ with time-varying optimal vaccination rate, shown in Figure 7, for various transmission coefficients, β_c and β_d

β_c, β_d	$J(v)$ with constant $v(t) = 0.3$	$J(v)$ with time-varying optimal v^*
10^{-6}	203	192
0.0007	1,224	1,216
0.007	6,416	6,416

Table 8

Comparison of $J(v)$ with constant vaccination rate to $J(v)$ with time-varying optimal vaccination rate, shown in Figure 10, for various upper bounds, M , on $v(t)$ with increased $\beta_c, \beta_d = 0.007$

M	$J(v)$ with constant $v(t) = M$	$J(v)$ with time-varying optimal v^*
0.3	6,416	6,416
0.6	6,433	6,398