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Vaccine. Author manuscript; available in PMC 2011 July 19.

Published in final edited form as:
Vaccine. 2010 July 19; 28(32): 5245–5253. doi:10.1016/j.vaccine.2010.05.062.

The Potential Value of *Clostridium difficile* Vaccine: An Economic Computer Simulation Model

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Abstract

Efforts are currently underway to develop a vaccine against *Clostridium difficile* infection (CDI). We developed two decision analytic Monte Carlo computer simulation models: (1) an Initial Prevention Model depicting the decision whether to administer *C. difficile* vaccine to patients at-risk for CDI and (2) a Recurrence Prevention Model depicting the decision whether to administer *C. difficile* vaccine to prevent CDI recurrence. Our results suggest that a *C. difficile* vaccine could be cost-effective over a wide range of *C. difficile* risk, vaccine costs, and vaccine efficacies especially when being used post-CDI treatment to prevent recurrent disease.

Keywords

Clostridium difficile; vaccine; economics; computer simulation

1. INTRODUCTION

Efforts are currently underway to develop a vaccine against *Clostridium difficile* infection (CDI), a major and potentially growing cause of substantial morbidity, costs, and mortality throughout the developed world [1-9]. Although numerous interventions have been implemented to control the spread of *Clostridium difficile* (*C. difficile*) in hospitals, the bacterial pathogen remains established in many locations and continues to spread to others. CDI can result in longer hospital length of stay, necessitate antibiotic use that may lead to more antibiotic-resistant bacteria, and even require surgical procedures. A significant

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percentage of treated patients may experience relapse of disease, in some cases multiple relapses [10]. Moreover, the recent emergence of more virulent strains may make combating the nosocomial pathogen even more difficult [11].

Candidate *C. difficile* vaccines currently are in pre-clinical and early clinical development and show promise as options for both preventing and treating CDI. A potential vaccine containing *C. difficile* toxoids A and B has been shown to induce immune response in healthy adults [12]. Antibody levels measured from study participants exceeded the level previously shown to be associated with CDI prevention [9]. There is also evidence that such a vaccine could effectively treat recurrent infections, particularly those that other methods have failed to remedy [8].

Constructing economic models early in a vaccine's development can help identify appropriate target populations, establish vaccine efficacy targets, assist in pricing and reimbursement decisions, and help determine the investment that should be made into developing the vaccine when substantial changes are still possible. A number of vaccines have faced challenges when economic modeling occurred too late in the vaccine timeline to make necessary changes [13]. To answer such questions regarding *C. difficile* vaccine, we constructed computer models to simulate the decision of whether to administer *C. difficile* vaccine to patients. One model simulated the choice of whether to perform universal vaccination on at-risk patients. A second model simulated the option of vaccinating those currently with CDI and undergoing antibiotic treatment to prevent recurrence. Sensitivity analyses explored how the economic value of the vaccine varied with CDI risk, vaccine cost, and vaccine efficacy.

2. METHODS

Using TreeAge Pro 2009 (TreeAge Software, Williamstown, MA), we developed two decision analytic Monte Carlo computer simulation models:

- Initial Prevention Model: depicting the decision whether to administer *C. difficile* vaccine to patients at-risk for CDI.
- Recurrence Prevention Model: depicting the decision whether to administer *C. difficile* vaccine to patients currently with CDI to prevent CDI recurrence.

The model assumed the societal, hospital, and third party payer perspectives and simulated the potential consequences of the decision.

Figure 1a illustrates the Initial Prevention Model structure. Each patient had a risk of *C. difficile* colonization based on the local *C. difficile* prevalence. Figures 1 and 2 showdifferent variable names as the probabilities of moving down each branch. These variable names correspond to the variable names in the second column of Table 1. For example, the variable pInf represents the probability of infection; its complement 1-pInf calculates the probability of no infection. The variable pInf draws from the distribution with the parameters indicated in Table 1. The median age of a patient was 71 years, the median age of patients discharged with a diagnosis of *C. difficile* from the 2007 National Inpatient Survey from the Healthcare Cost and Utilization Project [14]. Each colonized patient then entered into a *C. difficile* outcomes sub-tree. Colonized patients had probabilities of remaining as asymptomatic carriers or progressing to CDI. Figures 1b and 1c show the CDI outcome models for mild and severe CDI, respectively. Both mild and severe CDI required antibiotic treatment, which had probabilities of being effective. Ineffective treatment allowed progression to more severe infections, requiring surgery and potentially leading to death. Patients successfully treated with antibiotics could either remain free of disease or suffer a CDI recurrence, i.e., reappearance of CDI within three months of successful

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treatment. Those who had a successfully treated first recurrence could then have a second recurrence. Patients who suffered two or more recurrences that were unsuccessfully treated had a probability of progressing to a severe disease state requiring surgery.

Figure 2a depicts the main decision model for the Recurrence Prevention Model. For this model, the median patient age was also 71 years. Each patient began with successfully treated CDI and then had a probability of experiencing recurrent CDI. All recurrences had probabilities of progressing either to mild or severe disease. Figure 2b represents the outcome model for mild CDI, while Figure 2c represents the outcome model for severe CDI, with both forms of CDI requiring antibiotic treatment. An effectively treated patient could then suffer a second recurrence. Ineffective treatments at any point in the model allowed progression to more serious CDI that required surgery and could result in death.

Treatment options depended on the disease severity, prior treatments, and number of recurrences. For mild disease, metronidazole was the first-line antibiotic treatment, and vancomycin was the second-line. For severe disease, the treatment of choice was vancomycin along with intravenous metronidazole prior to surgery. When patients suffered a recurrence, the first-line treatment was the same antibiotic that worked for the initial CDI episode (e.g. a patient who relapsed after being successfully treated with metronidazole then received metronidazole again). Patients suffering two or more recurrences received a tapered course of vancomycin. Additionally, patients with severe disease required peripheral intravenous line insertion as well as an abdominal computerized tomography.

Our model measures effectiveness in disability-adjusted life years (DALYs) prevented using the following formula:

$$\mathrm{DALY}=\mathrm{YLL}+\mathrm{YLD}$$

Where YLL=Years Lost to Life and YLD=Years Lost to Disability.

For each simulation run, we determined the incremental cost effectiveness ratio (ICER) of *C. difficile* vaccination as defined as:

$$=\frac{\mathrm{Cost}_{Vaccination}-\mathrm{Cost}_{NoVaccination}}{-(\mathrm{DALYs}_{Vaccination}-\mathrm{DALYs}_{NoVaccination})}$$

Vaccination was considered to be cost-effective if the ICER fell below three times the per capita gross domestic product (GDP) or $80,412/DALY prevented for the United States, a frequently cited threshold for cost-effectiveness [15,16].

2.1 Data Inputs

Table 1 lists the input parameters for the model, including variable names (featured in the Figures), probabilities, costs, and utilities, as well as the distribution parameters for each variable. Probabilities assumed beta distributions, except for the efficacy of tapered vancomycin treatment (triangular distribution), as well as the probability of colonization and the probability of successful isolation, which were fixed values during each simulation. All costs were in 2009 U.S. dollars. A 3% discount rate adjusted all costs to 2009 dollars.

We used two separate approaches to determine the costs associated with CDI:

- *Health Care Resource Use:* A first approach involved identifying the procedure and hospitalization costs associated with different CDI conditions. Costs drew from triangular distributions, with several exceptions: costs of hospitalization,

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metronidazole [intravenous (IV) and oral (PO)], and surgery assumed gamma distributions, while the cost of in-hospital death was fixed at $5000.

- *Opportunity Cost of Lost Bed-Days:* An alternative approach re-conducted our analyses using a method described by Graves to ascribe economic costs to hospital infections [17]. When CDI caused a patient to occupy a bed for a longer period of time, the hospital lost revenue because the bed could have been filled by another patient. The Graves method involved valuing the opportunity cost of a lost bed day and then multiplying it by the extended hospital length-of-stay caused by the ensuing type of CDI.

Disability weights corresponding to diarrheal disease came from the World Health Organization's Global Burden of Disease [18]. CDI, CDI recurrences, and death each resulted in corresponding DALY increments (Table 1). The length of disease was six days, the median length of hospitalization for a 71-year-old patient with CDI.

2.2 Sensitivity Analyses

Because *C. difficile* risk may differ significantly from hospital-to-hospital, sensitivity analyses systematically varied the risk of *C. difficile* from 0.1% to 90%. Additional sensitivity analyses ranged vaccine efficacy from 25% to 100%. Because one of our goals is to estimate the cost thresholds under which a vaccine would remain cost-effective, we started vaccine cost at $25 for the Initial Prevention Model and $100 for the Recurrence Prevention Model. We then systematically increased the cost of the vaccine until it was no longer cost-effective. (Consequently, sensitivity analyses ranged vaccine cost from $25 to $100 in the Initial Prevention Model and from $100 to $1600 in the Recurrence Prevention Model.) Furthermore, probabilistic (Monte Carlo) sensitivity analyses simultaneously varied the values of each parameter throughout the ranges shown in Table 1. Another set of sensitivity analyses varied the probability of undergoing colectomy due to severe CDI from its baseline probability distribution listed in Table 1 down to 0.6% and 0.2%.

3. RESULTS

3.1 Health Care Resource Use Approach

Each simulation run comprised of a cohort of 5,000 patients, each travelling 5,000 times through the model for a total of 2,500,000 simulated trials. Table 2 displays the results from the Initial Prevention Model when varying *C. difficile* risk, vaccine efficacy, and vaccine cost. Shaded cells correspond to situations where vaccination is not cost-effective. Vaccination was economically dominant (both less costly and more effective) over no vaccination when *C. difficile* risk was at least 5% at almost every vaccine efficacy and cost combination, except when vaccine efficacy dropped to 25% and vaccine cost was at least $50 and when vaccine efficacy was 50% and cost was equal to $100. A $25 vaccine was dominant as long *as C. difficile* risk was at least 2.5%.

Table 3 shows results from the Recurrence Prevention Model at different vaccine efficacies and costs. Vaccination was cost-effective, and frequently economically dominant, in most situations. An $800 vaccine was dominant as long as vaccine efficacy was at least 50%. Even at a cost of $1600, a 75% efficacious vaccination was cost-effective.

Figure 3 displays acceptability curves at different prevalence levels with vaccine efficacy equal to 75% and cost of vaccine equal to $100 for the Initial Prevention Model. Each curve represents the proportion of patients per simulation for which vaccination was a more cost-effective strategy (optimal choice) over no vaccination at various willingness-to-pay (WTP) thresholds. For example, when *C. difficile* risk was 5%, vaccination was the optimal strategy

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for over 40% of patients regardless of the WTP threshold. When risk was 10%, vaccination was the optimal choice for over 60% of patients at all WTP thresholds. Figure 4 displays acceptability curves for the Recurrence Prevention Model at varying vaccine efficacy rates when the cost of vaccine was $800. When vaccine efficacy was 50%, vaccination was the optimal choice for 68% of patients at a WTP threshold of $0. When vaccine efficacy was 75%, vaccination was the optimal selection for over 90% of patients regardless of the WTP threshold. All results remained robust to (i.e., were not affected by) varying the probability of severe disease necessitating colectomy.

3.2 Opportunity Cost of Lost Bed-Day Approach

Each simulation run comprised of a cohort of 5,000 patients, each travelling 5,000 times through the model for a total of 2,500,000 simulated trials. Table 4 presents the results for the Initial Prevention Model at varying *C. difficile* risk, vaccine efficacies, and vaccine costs. Vaccination was cost-effective when vaccine cost was $25 and *C. difficile* risk was equal to or greater than 10%, except when efficacy was 25% and *C. difficile* risk was less than or equal to 15%.

Table 5 lists the cost-effectiveness of vaccination for the Recurrence Prevention Model. Vaccination was cost-effective at all vaccine efficacy and cost combinations except when cost was equal to $800 and efficacy was equal to or less than 50% and when cost was equal to $400 and efficacy was equal to 25%. Vaccination became dominant when the cost of vaccine was $200 or less, except when efficacy dropped to 50% at vaccine cost $200 and 25% at vaccine cost $100. All results remained robust to varying the probability of colectomy.

4. DISCUSSION

C. difficile vaccination appears to be cost-effective for a wide range of *C. difficile* risk, vaccine efficacies, and vaccine costs. In fact, vaccination quickly becomes economically dominant as *C. difficile* risk and vaccine efficacy increase, suggesting that vaccination in some settings could actually save society, third party payers, and hospitals money while preventing morbidity and mortality. Economically dominant interventions are not common in health care, as many measures require some cost to prevent morbidity and mortality. Therefore, finding an intervention to be cost saving in addition to beneficial to health strongly supports its implementation. So, while the risk of *C. difficile* may vary significantly from health care facility-to-health care facility and patient-to-patient, vaccination may be favorable in many circumstances. This is compelling evidence for policymakers and researchers to further invest in the development of *C. difficile* vaccine.

If and when a *C. difficile* vaccine reaches the market, choosing an appropriate target population will be important. Even effective vaccines such as the Lyme disease vaccine have struggled when target populations were not selected carefully [13]. Our results suggest that preventing CDI recurrence may be good initial indication for the vaccine. This initial indication could support even higher vaccine prices, which may provide further motivation for manufacturers to bring the vaccine to market. As expected, broader use for the initial prevention of CDI may not support as high prices, but increased volume may compensate for lower prices. Our results also outlined possible effects of using various *C. difficile* risk thresholds if vaccination is to be restricted to higher-risk individuals.

The potential value of the vaccine stems from the heavy burden of CDI. Even mild disease such as diarrhea, abdominal pain, and nausea can add to costs and lengthen hospital stay. More severe conditions such as fever, severe shock or sepsis, and toxic megacolon can result in expensive procedures and may even lead to death. The biology of *C. difficile* makes it a

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difficult pathogen to control; *C. difficile* spores are resistant to heat, ethanol-based hand sanitizers, and quaternary ammonium disinfectants and can survive for months without proper disinfection [1]. In fact, *C. difficile* may be a growing problem. From 1993 to 2003, both the number of *C. difficile* cases and deaths more than doubled in the United States (cases went from 261 to 546 cases and deaths went from 20.3 to 50.2 per 100,000 discharged patients) [19]. Moreover, recent years have seen the emergence of a hypervirulent *C. difficile* strain [11].

Certainly, developing a functional *C. difficile* vaccine faces some technological challenges [20-22]. A parenteral or intravenous vaccine candidate may stimulate the production of circulating antibodies in the bloodstream but not adequately protect the gastrointestinal mucosa, where the pathogen inflicts most of its damage. Inducing complete mucosal protection (e.g., stimulating gut-associated lymphoid tissue) may require the stimulation of all immune system arms, including mucosal secretory IgA, functional serum IgG antibodies, and systemic and local cell-mediated immune responses. Direct local delivery of an adequate dose to the gastrointestinal mucosa may be possible but not necessarily easy. Achieving adequate protection may require an initial priming dose and then subsequent booster doses. Nonetheless encouraging advances in mucosal immunization have occurred over the past decade. Flumist (a live attenuated influenza vaccine), the Sabin oral polio vaccine, Ty21a (for typhoid fever), CVD 103-HgR (for cholera), and RotaTeq (for rotavirus infection) are examples of licensed and effective mucosally administered vaccines.

Our intent was to be conservative and err on the side of underestimating the benefits of a *C. difficile* vaccine. Our model included only the more common CDI sequelae and, when choices were available, the less expensive procedures. It also excluded chronic disease exacerbations that CDI may induce (e.g., dehydration leading to diabetic ketoacidosis in a diabetic) and relatively rare *C. difficile* complications. In addition, our model did not incorporate how vaccination could prevent *C. difficile* transmission or reduce the selection pressure for antibiotic-resistant bacteria (such as vancomycin-resistant *Staphylococcus aureus*) by minimizing the use of antibiotics to treat CDI. Moreover, combining vaccine with other infection control measures (e.g., hand hygiene and cohorting) could have compounding effects in controlling *C. difficile* spread.

4.1 Limitations

All computer models are simplifications of real life and cannot completely represent every possible *C. difficile* and CDI-associated factor, event, and outcome. Computer models also cannot fully represent the full spectrum of socio-demographic and clinical heterogeneity among hospital patients and hospitals. Additionally, as stated earlier, our model focused on more common clinical outcomes for which data were available and did not incorporate all of the potential benefits of vaccination. Finally, the data inputs for our model derived from different studies of varying quality.

4.2 Conclusions

Once developed, a *C. difficile* vaccine could be cost-effective over a wide range of *C. difficile* risk, vaccine costs, and vaccine efficacies. The vaccine could be particularly valuable for patients currently treated for CDI to prevent recurrent disease. Our study results support further investment into developing a *C. difficile* vaccine and suggest that vaccine efficacy targets do not necessarily have to be exceptionally high for the vaccine to have value. Our results also identified possible price points for the vaccine to assist manufacturers, third party payers, and other potential purchasers.

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Acknowledgments

This study was supported by the National Institute of General Medical Sciences Models of Infectious Agent Study (MIDAS) grant 1U54GM088491-0109, the Pennsylvania Department of Health, and the Vaccine Modeling Initiative (VMI), funded by the Bill and Melinda Gates Foundation. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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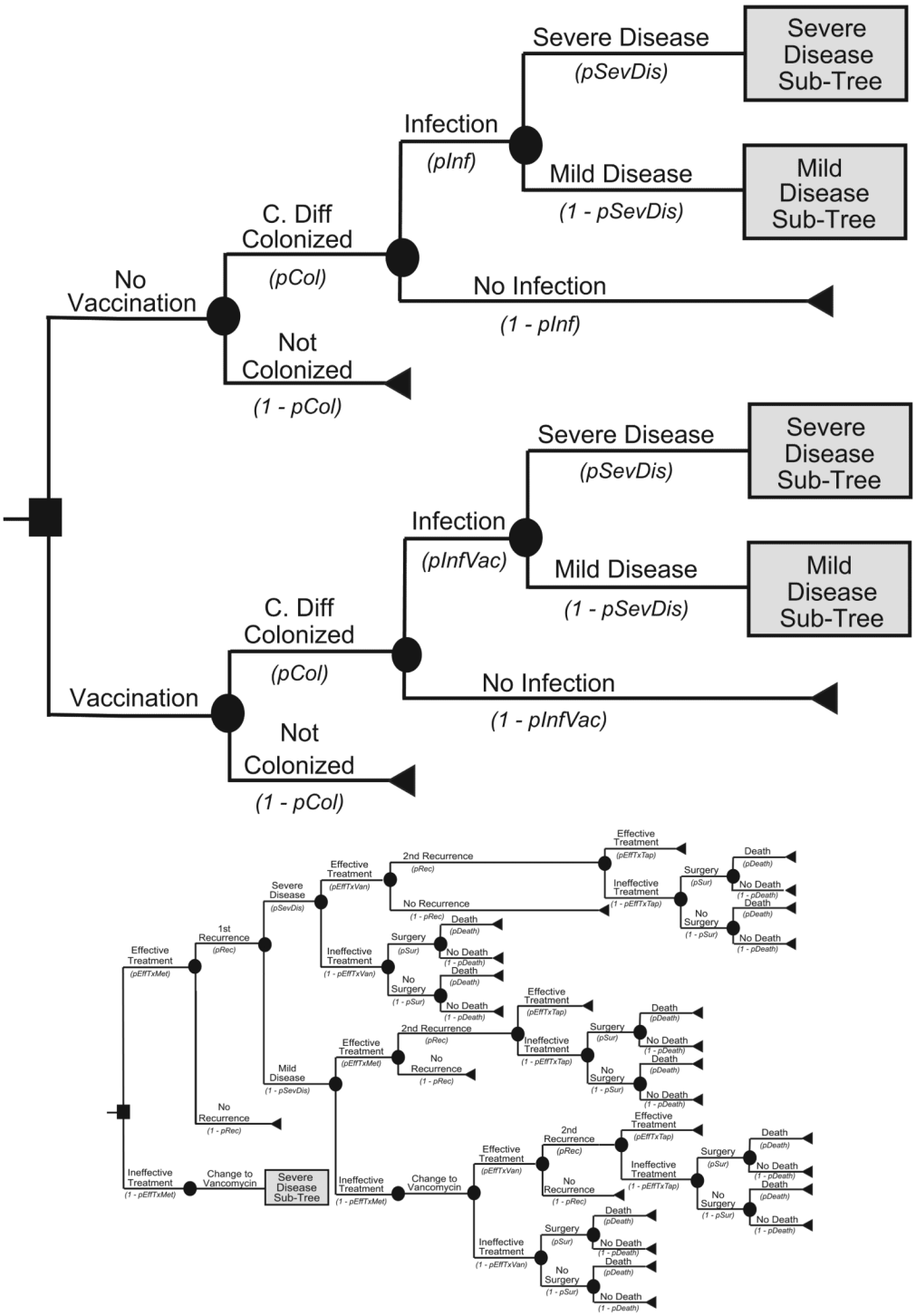

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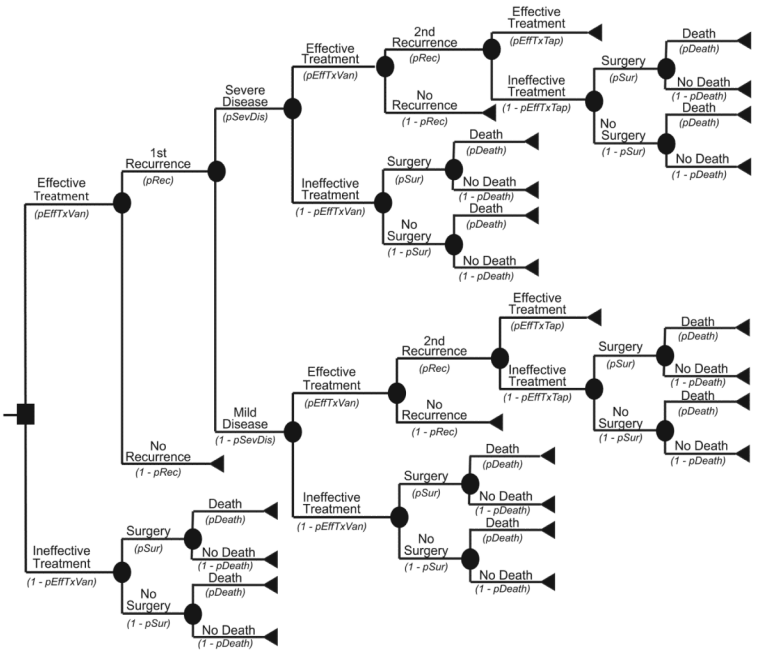

FIGURE 1.

FIGURE 1a: Initial Prevention Main Model Structure

FIGURE 1b: Initial Prevention Mild Disease Outcomes Sub-Tree Structure

FIGURE 1c: Initial Prevention Severe Disease Outcomes Sub-Tree Structure

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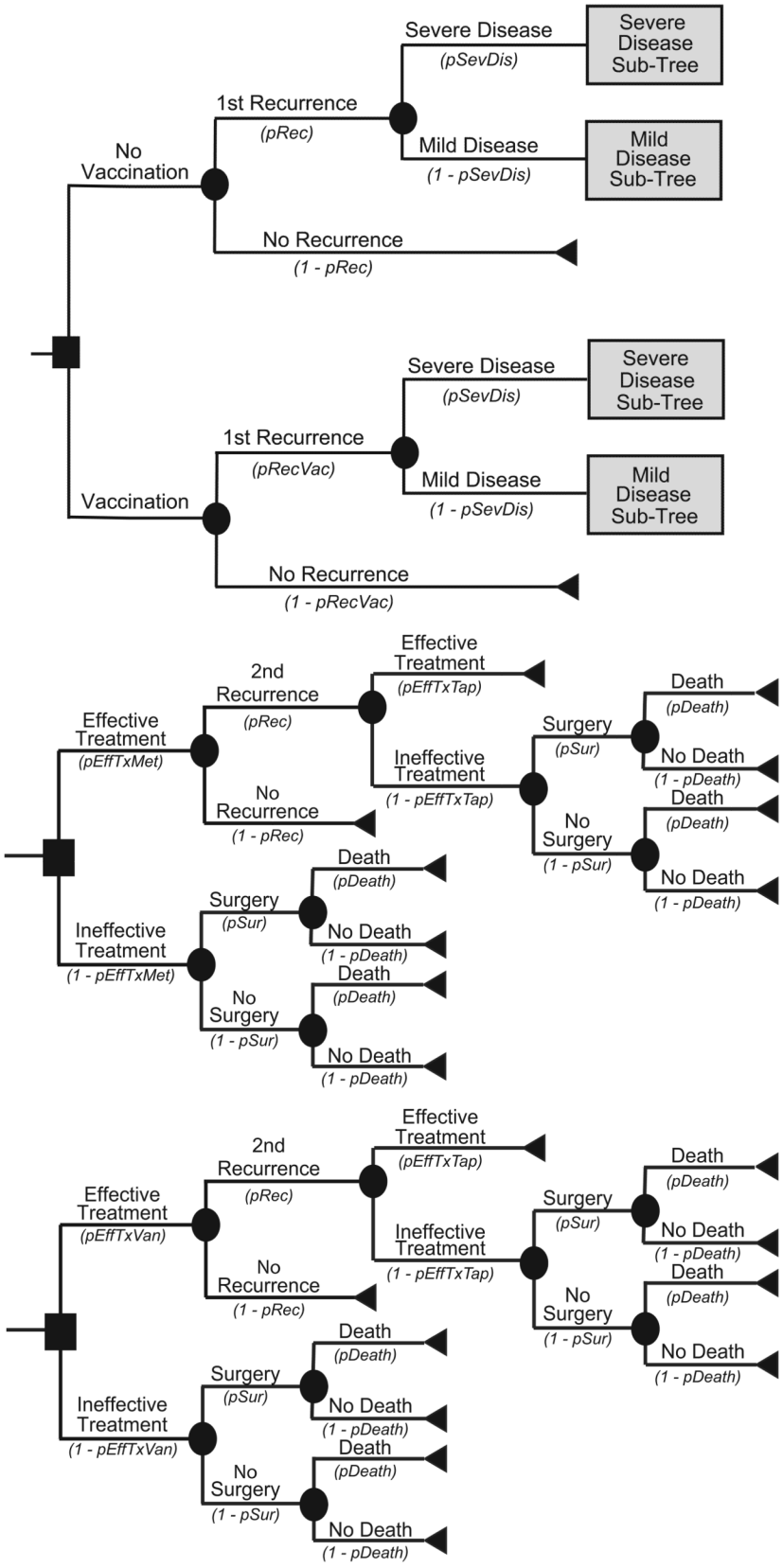

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FIGURE 2.

FIGURE 2a: Recurrence Prevention Main Model Structure

FIGURE 2b: Recurrence Prevention Mild Disease Outcomes Sub-Tree Structure

FIGURE 2c: Recurrence Prevention Severe Disease Outcomes Sub-Tree Structure

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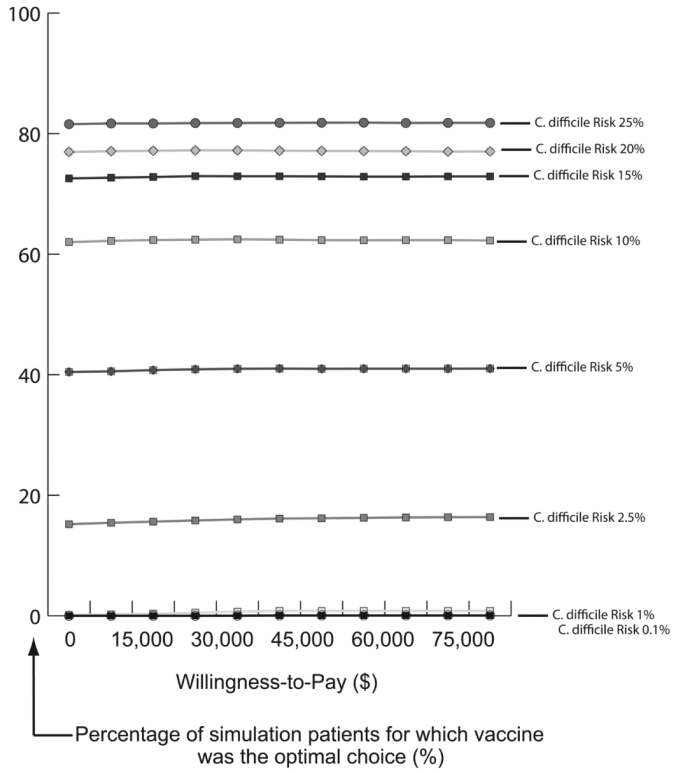

FIGURE 3.

Acceptability Curves at Different *C. difficile* Risk for Vaccine Efficacy of 75% and Cost of Vaccination of $100 for Initial Prevention

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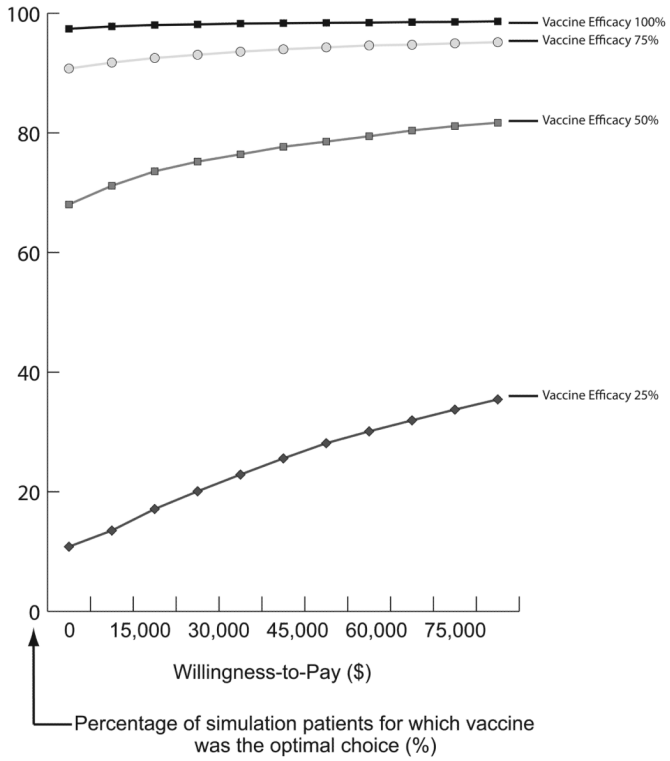

FIGURE 4.

Acceptability Curves at Different *C. difficile* Vaccine Efficacy for Cost of Vaccination of $800 for Recurrence Prevention

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TABLE 1

Data Inputs for Model Variables

Description (units)	Variable Name	Median	Upper Limit (or SD[a])	Lower Limit	Source
COSTS ($US)					
Abdominal CT Scan		1535.58	1013.48	2057.68	23
Hospitalization		7517.54	242.95[a]		14
Metronidazole (IV)		107.86	10.28[a]		24
Metronidazole (PO)		60.90	39.28[a]		24
Peripheral Intravenous Line Insertion		146.25	96.52	195.98	25
Surgery (Colectomy)		15995.10	5412.71[a]		14
Vancomycin		1184.90	782.03	1587.77	24
Vancomycin (Tapered)		2221.70	1466.32	2977.07	24
UTILITIES (DALYs)					
1st Recurrence		−0.0029	−0.0039	−0.0019	18
2nd+ Recurrences		−0.0043	−0.0058	−0.0029	18
C. difficile Infection		−0.0014	−0.0019	−0.0009	18
Mortality		−14.00	−18.76	−9.24	18
PROBABILITIES (%)					
Given C. difficile colonization:					
Developing *C. difficile* infection	pInf	26.15	25.69[a]		26-29
Given C. difficile infection:					
Mortality	pDeath	2.66	2.13[a]		14, 30-32
Recurrence	pRec	20.00	6.77[a]		33-35
Severe Disease	pSevDis	8.09	13.05[a]		30, 36, 37
Mild Disease		91.91[b]	*b*		30, 36, 37
Surgery (Colectomy)	pSur	1.20	2.51[a]		19, 30, 34, 38-42
C. difficile treatment efficacies:					
Metronidazole	pEffTxMet	90.41	9.28[a]		43-50

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Description (units)	Variable Name	Median	Upper Limit (or SD[a])	Lower Limit	Source
Vancomycin	pEffTxVan	98.18	7.64[a]		45, 46, 48-53
Vancomycin (Tapered)	pEffTxTap	68.97	45.52	92.41	54

[a] Standard deviation.

[b] Probability of mild disease is calculated as 1 - pSevDis

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TABLE 2

Incremental Cost-Effectiveness Ratio ($US/DALY prevented) of Vaccination for Initial Prevention of *Clostridium difficile* infection (CDI) using the Health Care Resource Use Approach.

Vaccine Efficacy	*Clostridium difficile* Risk							
	0.1%	**1.0%**	**2.5%**	**5.0%**	**10.0%**	**15.0%**	**20.0%**	**25.0%**
25%	12,697,913	4,189,295	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
50%	11,832,473	1,320,623	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
75%	5,429,310	445,746	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
100%	1,420,236	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
25%	28,084,233	4,329,877	2,176,586	727,421	Dominant	Dominant	Dominant	Dominant
50%	26,917,206	4,074,365	522,459	Dominant	Dominant	Dominant	Dominant	Dominant
75%	21,388,859	2,256,369	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
100%	12,064,352	887,840	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
25%	117,638,162	29,845,039	4,258,047	3,664,621	751,912	2,169	Dominant	Dominant
50%	66,314,756	7,378,601	1,783,465	478,200	Dominant	Dominant	Dominant	Dominant
75%	59,743,367	4,459,509	1,646,619	Dominant	Dominant	Dominant	Dominant	Dominant
100%	41,956,115	3,483,069	539,666	Dominant	Dominant	Dominant	Dominant	Dominant

NOTE: Dominant = Vaccination is the dominant strategy (i.e., less costly and more effective)

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TABLE 3

Incremental Cost-Effectiveness Ratio ($US/DALY prevented) of Vaccination for *Clostridium difficile* infection (CDI) Recurrence Prevention of using the Health Care Resource Use Approach.

Vaccine Efficacy	Cost of Vaccination				
	$1600	**$800**	**$400**	**$200**	**$100**
25%	354,064	92,691	Dominant	Dominant	Dominant
50%	94,054	Dominant	Dominant	Dominant	Dominant
75%	5,081	Dominant	Dominant	Dominant	Dominant
100%	Dominant	Dominant	Dominant	Dominant	Dominant

NOTE: Dominant = Vaccination is the dominant strategy (i.e., less costly and more effective)

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TABLE 4

Incremental Cost-Effectiveness Ratio ($US/DALY prevented) of Vaccination for Initial Prevention of *Clostridium difficile* infection (CDI) using the Opportunity Cost of Lost Bed-Days Approach.

Vaccine Efficacy	*Clostridium difficile* Risk							
	0.1%	**1.0%**	**2.5%**	**5.0%**	**10.0%**	**15.0%**	**20.0%**	**25.0%**
25%	102,512,396	5,802,049	3,150,365	670,243	219,928	159,819	51,886	9,750
50%	7,835,447	1,774,240	1,120,416	235,026	46,099	Dominant	Dominant	Dominant
75%	9,242,325	1,135,269	437,496	125,266	Dominant	Dominant	Dominant	Dominant
100%	13,588,967	1,114,979	300,389	56,679	Dominant	Dominant	Dominant	Dominant
25%	355,495,778	9,495,689	4,775,304	1,901,144	697,507	419,099	312,448	189,174
50%	62,561,269	3,928,690	2,619,269	674,142	260,932	130,529	54,358	5,540
75%	38,053,933	3,606,097	1,274,169	448,297	134,118	29,308	Dominant	Dominant
100%	31,053,420	2,377,616	755,625	271,070	46,872	Dominant	Dominant	Dominant
25%	397,800,954	14,296,136	13,956,184	2,151,773	1,241,526	1,089,628	878,411	949,495
50%	121,217,228	7,336,363	2,797,316	1,645,005	885,973	436,334	277,371	196,372
75%	99,166,559	6,559,099	2,093,538	994,250	421,389	227,919	143,188	68,418
100%	34,978,919	6,098,157	1,590,522	695,307	285,349	147,266	54,144	10,528

NOTE: Dominant = Vaccination is the dominant strategy (i.e., less costly and more effective)

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TABLE 5

Incremental Cost-Effectiveness Ratio ($US/DALY prevented) of Vaccination for *Clostridium difficile* infection (CDI) Recurrence Prevention using the Opportunity Cost of Lost Bed-Days Approach.

Vaccine Efficacy	Cost of Vaccination				
	$800	**$400**	**$200**	**$100**	**$50**
25%	243,994	107,576	42,704	9,247	Dominant
50%	111,054	42,259	9,653	Dominant	Dominant
75%	66,756	21,121	Dominant	Dominant	Dominant
100%	43,500	8,919	Dominant	Dominant	Dominant

NOTE: Dominant = Vaccination is the dominant strategy (i.e., less costly and more effective)

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