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ORIGINAL ARTICLE

Assessing control bundles for *Clostridium difficile*: a review and mathematical model

Laith Yakob[1], Thomas V Riley[2], David L Paterson[3], John Marquess[1] and Archie CA Clements[4]

Clostridium difficile **is the leading cause of infectious diarrhea in hospitalized patients. Integrating several infection control and prevention methods is a burgeoning strategy for reducing disease incidence in healthcare settings. We present an up-to-date review of the literature on 'control bundles' used to mitigate the transmission of this pathogen. All clinical studies of control bundles reported substantial reductions in disease rates, in the order of 33%–61%. Using a biologically realistic mathematical model we then simulated the efficacy of different combinations of the most prominent control methods: stricter antimicrobial stewardship; the administering of probiotics/intestinal microbiota transplantation; and improved hygiene and sanitation. We also assessed the health gains that can be expected from reducing the average length of stay of inpatients. In terms of reducing the rates of colonization, all combinations had the potential to give rise to marked improvements. For example, halving the number of inpatients on broad-spectrum antimicrobials combined with prescribing probiotics or intestinal microbiota transplantation could cut pathogen carriage by two-thirds. However, in terms of symptomatic disease incidence reduction, antimicrobials, probiotics and intestinal microbiota transplantation proved substantially less effective. Eliminating within-ward transmission by improving sanitation and reducing average length of stay (from six to three days) yielded the most potent symptomatic infection control combination, cutting rates down from three to less than one per 1000 hospital bed days. Both the empirical and theoretical exploration of** ***C. difficile*** **control combinations presented in the current study highlights the potential gains that can be achieved through strategically integrated infection control.**
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Keywords: epidemiology; healthcare-acquired infection; infection control bundle; transmission model; nosocomial; stochastic simulation

INTRODUCTION

Clostridium difficile is the leading cause of infectious diarrhea in hospitalized patients. Although highly variable between countries, the worldwide incidence and severity of *C. difficile* infection (CDI) have increased in recent years,[1–3] with a higher proportion of CDI patients undergoing colectomy and dying.[4,5] The disease is currently estimated to cost $800 million per year in US acute care facilities.[6] Of particular concern are epidemic strains of the pathogen that have emerged in recent years and that incur high mortality rates.[7] While the disease has traditionally been associated with healthcare facilities of the industrialized world, it is increasingly recognized as a major contributor to healthcare-acquired infections in developing countries.[8] Studies in Argentina, Chile, India and Iran have shown a consistently high prevalence of CDI (6%–17%) in inpatients.[9–12]

Until recently, disturbance of the intestinal microbiota resulting from antimicrobials was considered a prerequisite of the disease. However, the epidemiological picture of CDI has been obscured following increased reports of transmission within the community and severe cases occurring in previously low-risk groups, including pregnant women, children and people with no recent exposure to antimicrobials.[13,14] An increased frequency of newly emergent epidemic strains has also been described.[7] For both endemic and epidemic strains of *C. difficile*, healthcare facilities act as infection transmission hubs and, therefore, provide obvious targets for intervention.

Although published studies detailing the simulated pathogen transmission dynamics are relatively few in number, almost all have explored the anticipated effects of different interventions.[15–18] These different models with different underlying structures and methods of analysis have yielded a good level of agreement in their projections. In short, their projections agree over the health benefits that can be expected from increased hygiene and sanitation practices within hospitals in order to reduce *C. difficile* transmission potential.

To date, no study has systematically analyzed the clinical literature for the level of health gains that can be expected from integrating the numerous available control methods. This is surprising given the multicomponent strategies that are routinely employed to combat the spread of disease in hospitals. The Association for Professionals in Infection Control and Epidemiology currently describe a suite of recommendations for preventing CDI.[19] Given the recognized major role of the environment in transmission,[20] contact precautions are recommended through segregating CDI from non-CDI patients; limiting patient movement through the healthcare facility; vigilant equipment disinfection; and wearing isolation gowns and gloves for each patient encounter. Related to this latter measure, strict adherence to

[1]The University of Queensland, School of Population Health, Herston 4006, Australia; [2]The University of Western Australia, School of Pathology and Laboratory Medicine, Crawley 6009, Australia; [3]The University of Queensland, Centre of Clinical Research, Herston 4029, Australia and [4]The Australian National University, Research School of Population Health, Canberra 0200, Australia
Correspondence: L Yakob
E-mail: laith.yakob@uq.edu.au
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hand hygiene protocols by staff, patients and visitors, and, proper environmental decontamination are further recommended interventions. From a modeling perspective, all of these measures will have the function of reducing within-hospital ward infection transmission potential.

The Association for Professionals in Infection Control and Epidemiology also recommends antimicrobial stewardship as another important component of infection prevention. This is defined as the avoidance of prolonged empiric therapy, targeting therapy by narrowing the spectrum of antimicrobial action, ensuring that the appropriate dosage and duration of therapy are used, and then discontinuing therapy as soon as possible. Because antimicrobial exposure is the primary risk factor associated with CDI development,[21] stewardship is expected to attenuate infection rates by reducing the overall susceptibility of hospital patients. These guidelines essentially reiterate the general recommendations of multifactorial infection control measures as described in preceding guidelines.[22–24]

Our aim is to explore effective strategies for combining *C. difficile* control measures in order to develop an infection control framework that capitalizes upon a multipronged interruption of the pathogen's transmission. First, we review the clinical literature for evidence to support (or refute) the additional efficacy in reducing *C. difficile* burden by combining different controls. Then we describe a stochastic, event-driven mathematical model of *C. difficile* transmission (adapted and updated from reference 25) and use it to simulate several control combinations—including both standard and novel control measures. The model is used to inform improved efficacy in infection control practices within healthcare facilities.

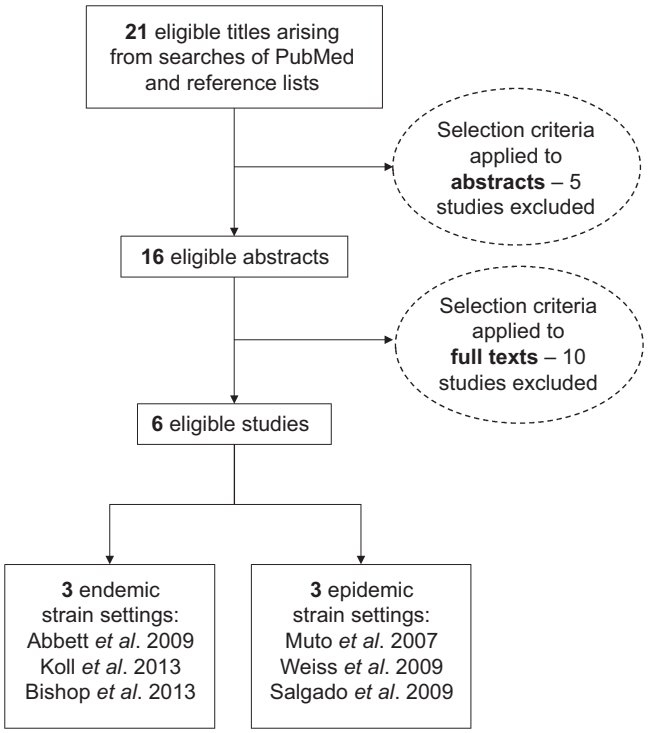

Figure 1 Flow chart of selection process to identify relevant studies assessing the efficacy of *C. difficile* control bundles.

MATERIALS AND METHODS

Literature search strategy and study selection

A search was conducted of all relevant articles published up until March 2014, identified from the PubMed database. Key terms used in the search strategy included: '*Clostridium difficile* or *C. difficile*' and 'bundle or multiple control or control package or integrated control or multipronged or multi-pronged'. Review of bibliographies of papers was also carried out to ensure completeness of inclusion of all relevant clinical studies. Studies eligible for inclusion were those describing patient levels of symptomatic *C. difficile* infection before and after the implementation of multiple, overlapping infection transmission interventions. Articles that involved formalized strategies for enhancing the rates of multiple, pre-existing controls were included along with reports describing the introduction of control methods that were previously absent from the study setting (Figure 1). We discuss the outcome of this literature search in conjunction with results from our stochastic simulations of bundle approaches to controlling *C. difficile*.

C. difficile and its transmission

C. difficile is a gram-positive toxin-producing anaerobic bacterium transmitted via the fecal-oral route. While disturbed gut microbiota resulting from exposure to broad-spectrum antimicrobials is the prevailing predisposing factor,[26] this is no longer believed to be a prerequisite for the successful colonization of the gut.[27] Hence, there are two alternative routes of infection: one in an antimicrobial-treated, predisposed subpopulation and the other in a subpopulation of individuals that have not recently received treatment with antimicrobials. The inclusion of these parallel routes of bacterial colonization is key to understanding the modern epidemiology of *C. difficile*. The following section describes the compartmental framework that maps out the connections between the different epidemiological groups of patients in an acute healthcare facility. This mathematical model is then used to assess different integrated control strategies (or, 'control bundles') for reducing the transmission of *C. difficile* and ameliorating the burden of associated disease.

The mathematical model

We adapted our recently published model of *Clostridium difficile* transmission dynamics[25] to account for an increased level of biological realism before simulating different control combinations (the new model structure is shown in Figure 2 and the further improvements made to this model are detailed throughout the model description). The ordinary differential equations describing the instantaneous rates of change between the seven possible epidemiological states are as follows:

$$\frac{dU}{dt} = \xi_U \varphi + \lambda U_v + (1-\varepsilon)\theta C - \beta \frac{(C+C_v)U}{N} - (\alpha+\kappa)U$$

$$\frac{dU_v}{dt} = \xi_{U_v} \varphi + \alpha U + (1-\sigma)\rho(1-\zeta)D - \beta \frac{(C+C_v)U_v}{N} - (\lambda+\kappa)U_v$$

$$\frac{dE}{dt} = \xi_E \varphi + \lambda E_v + \beta \frac{(C+C_v)U}{N} - (\alpha+\eta+\kappa)E$$

$$\frac{dE_v}{dt} = \xi_{E_v} \varphi + \alpha E + \beta \frac{(C+C_v)U_v}{N} + \sigma\rho(1-\zeta)D - (\lambda+\eta+\kappa)E_v$$

$$\frac{dC}{dt} = \xi_C \varphi + \lambda C_v + \eta E - (\alpha+\theta+\kappa)C$$

$$\frac{dC_v}{dt} = \xi_{C_v} \varphi + \alpha C + \eta E_v + \tau\zeta D - (\lambda+\theta_v+\kappa)C_v$$

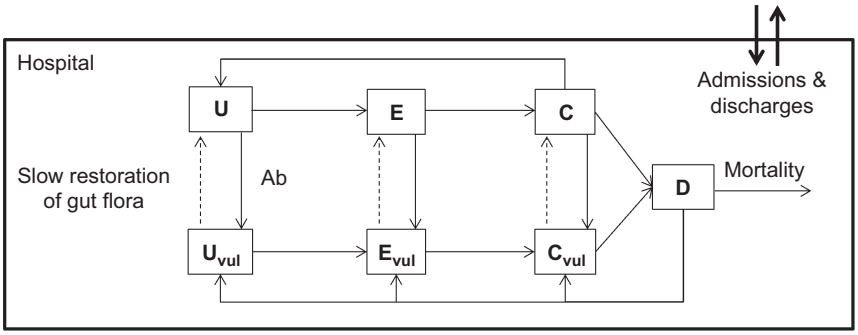

Figure 2 Compartmental design of the stochastic, event-driven mathematical model of *C. difficile* transmission within a simulated 1000-bed acute care hospital.

$$\frac{dD}{dt} = \xi_D\varphi + \varepsilon\theta C + \theta_v C_v - [\tau\zeta + \rho(1-\zeta) + \mu(1-\zeta)]D$$

Here, the total hospital inpatient population, $N = U + Uv + E + Ev + C + Cv + D$, was maintained at 1000 (assuming that a hospital bed is filled more or less as soon as it is emptied). Roman letters denote the number of individuals in the given state and Greek letters denote rates (and proportions) of change. '*U*'nexposed individuals become '*E*'xposed to *C. difficile* before they are asymptomatically '*C*'olonized, and, subsequently, symptomatically '*D*'iseased. There are two subpopulations described by the equations, differentiating individuals who have, and who have not, recently taken broad-spectrum antimicrobials. Infection in individuals who have not recently taken antimicrobials is a key feature of the modern epidemiology of *C. difficile* and is believed to have come about through the successful spread of hypervirulent strains.[7,28] The subscript 'v' denotes the groups that are currently taking, or have recently taken antimicrobials, and are more vulnerable to CDI progression than those who are not exposed to antimicrobials. The pathogen transmission coefficient is denoted β. Following exposure to *C. difficile* spores, it takes an average of five days ($\eta^{-1}=5$) before patients become asymptomatically colonized and infectious.[29] Following recent evidence, antimicrobial use does not increase the likelihood of colonization.[30] Predisposed patients consist of those that are currently on antimicrobials, or whom have taken antimicrobials in the preceding three months. This predisposed group is assumed to make up 50% of all inpatients.[31,32] Progression to symptomatic disease (CDI) takes five days ($\theta^{-1}=5$) following colonization and is five times more likely for predisposed patients ($\varepsilon^{-1}=5$).[30] In other words, the key mechanisms by which vulnerable and normal inpatients differ are the proportion of colonized individuals who become symptomatic and the rate at which they become symptomatic (which is higher for those who have been recently exposed to antimicrobials). This enhanced biological realism is a key distinguishing feature between this current model and previously published models including our own previous simulation model.[25]

Patient admissions, φ, were assumed to perfectly balance discharges summed with CDI deaths ($\varphi = \kappa(N-D) + \mu(1-\zeta)D$, assuming a constant hospitalized population) and were split proportionally across the different epidemiological categories according to ξ (with corresponding subscripts). Discharge rates were calculated simply as the inverse of the average length of stay, assumed to be 6 days.[33] Patients can be newly admitted in any epidemiological state but can only be discharged if they are not symptomatically infected. Patients can switch from non-predisposed to predisposed at rate α (accounting for the rate of antimicrobial prescription) and λ denotes the reverse process whereby a patient's gut microbiota recovers following discontinued antimicrobial use—assumed to take approximately three months.[34] It is assumed that the administering of probiotics or intestinal microbiota transplantation acts by expediting this recovery rate.[35,36] The symptoms of 33% of patients with CDI are assumed to self-resolve[37] within 2 days,[38] reflecting the high percentage of mild symptoms reported for this infection.[39] This rapid self-resolution of the significant percentage of CDI sufferers with milder symptoms is another element of enhanced biological realism that distinguishes this model from all previous simulation analyses.

CDI treatment (ρ^{-1}) takes 10 days[40] with an unsuccessful clearance rate, σ, of 20% per treated patient.[41] 6.8% of CDI sufferers die within 60 days of symptoms onset (the daily mortality rate, μ, is therefore calculated as $[1-(1-0.068)^{(1/60)}]=0.0012$).[30] This mortality rate is only experienced by the patients who suffer more severe symptoms—a logical and novel inclusion to this model. Symptomatic infection is itself treated with antimicrobials and, because of the damaged gut microbiota associated with symptoms, patients remain in vulnerable categories post-treatment. CDI sufferers are immediately quarantined from other inpatients and so do not contribute to transmission. While this does represent an optimistic simplification of the epidemiological system, our previous analyses have shown that within-hospital transmission is insensitive to a wide range of simulated screening/isolation levels.[25] The model parameters and associated studies are described in Table 1.

Using the methods outlined by Keeling and Rohani[42] this deterministic set of equations was converted into an event-driven Direct Gillespie simulation system.[43] Stochasticity incorporation is justified by the low prevalence of symptomatic infection harbored by the small simulated population.[42] This stochastic simulation model was then run until steady state (1000 days) and used to explore the effects of different integrated control scenarios.

Simulated colonization and disease interventions

Four control methods were explored in this analysis: (i) improved hand hygiene and sanitation; (ii) stricter antimicrobial stewardship; (iii) reduced length of stay (LoS) for inpatients; and (iv) expedited gut microbiota recovery which can be achieved either through administering probiotics or through intestinal microbiota transplantation. Antimicrobial stewardship can be interpreted as a reduction in rates of prescribed broad-spectrum antimicrobials that are known to be risk factors of *C. difficile* infection.[44] While the first two control methods represent quite typical control methods for attenuating the spread of nosocomial infections, LoS reduction, probiotics and intestinal microbiota transplantation are not typically included in intervention

Table 1 Epidemiological model symbology and parameterization

Symbol	Definition	Value (,vulnerable)	Control range	Reference
η	Develop into asymptomatic infectious (day^{-1})	0.2,0.2		34
$1-\varepsilon$	Colonization clearance in non-vulnerable (prop.)	0.8		30
θ	Develop symptomatic CDI (day^{-1})	0.04,0.2		30
ζ	CDI self-resolve (proportion of cases)	0.33		37
τ	CDI self-resolve rate (day^{-1})	0.5		38
ρ	CDI treatment (day^{-1})	0.1		40
σ	Treatment failure (proportion)	0.2		41
ξ	Hospital admission (proportion)	0.75,0.25		31,32
μ	Mortality rate (day^{-1})	0.0012		30
Simulated control				
λ	Recovery of gut flora (day^{-1})	0.011	0.011–0.1	34
α	Antimicrobial treatment (day^{-1})	0.1	0–0.1	31,32
β	Transmission coefficient (day^{-1})	0.5	0–1	
κ	Hospital discharge (day^{-1})	0.17	0.17–0.34	33

strategies. We included LoS reduction because of the strong impetus of clinicians and hospital managers to limit inpatient duration following evidence of LoS as a key risk factor for healthcare acquired infection.[45,46] We included probiotics and intestinal microbiota transplantation (also referred to as 'fecal bacteriotherapy') following the strong evidence in recent systematic reviews supporting the protective effect that they can have against *C. difficile*.[36,47]

Previous studies demonstrated the utility of improved sanitation and reduced average length of stay in reducing the transmission potential of *C. difficile*. Therefore, we began by exploring the effects of coupling these control tools. Most theoretical studies published to date have downplayed the efficacy of antimicrobial stewardship in reducing *C. difficile* transmission, but none has ascertained whether there are any additional benefits of complementing this strategy with the prescription of probiotics (both strategies might be expected to operate in the same epidemiological direction by reducing the proportion of inpatients that have heightened predisposition to CDI). All other combinations of the four control tools were simulated to ensure that no unexpected synergistic interactions were missed.

RESULTS

Clinical studies of the efficacy of bundles in controlling *C. difficile*

In 2000, an outbreak investigation recommended the sequential introduction of control measures and the development of a comprehensive *C. difficile* infection control 'bundle'. The successful implementation of this bundle consisting of antimicrobial stewardship and improved hospital-wide sanitation was subsequently reported by Muto and colleagues.[48] The authors describe a 58% reduction in the annual rate of *C. difficile* through the use of combined controls. Despite recommendations for integrated control existing in the literature for nearly two decades, studies pertaining to the benefits of a combination approach to control have been scant since the study of Muto *et al.*[48]

Following the NAP1/027 epidemic in Quebec in 2002, Weiss and colleagues conducted a five-year 'multipronged' *C. difficile* control strategy in an acute care tertiary hospital (the largest medical centre) in Quebec.[49] The strategy included rapid *C. difficile* testing of patients with unformed stools (with subsequent isolation of test-positives), a global hand hygiene program and the hiring of a team of infection control practitioners. They observed a 61% reduction in CDI rates over the study period.[49] Abbett *et al.*[50] and Salgado *et al.*[51] describe the use of a *C. difficile* prevention bundle in their university-affiliated tertiary care facilities. They also report encouraging reductions (of 40% and 45% respectively) in CDI rates over the study period through the use of rapid isolation of test-positives and enhanced infection control practices including escalated environmental cleaning. A collaborative effort of 35 New York metropolitan area healthcare facilities showed a statistically significant combined reduction in CDI rates (approximately 30%) following the implementation of an infection control bundle comprising of segregation of CDI patients, improved hygiene practice and enhanced environmental cleaning.[52] Bishop *et al.*[53] recently documented a similar reduction level (36%) in CDI case numbers following implementation of a bundle approach to controlling infection in surgical inpatients. Hence, the relatively few studies detailing a bundle approach to *C. difficile* control indicate substantial reductions in disease incidence in healthcare settings (Table 2 summarizes the findings of all relevant studies).

However, these combination control assessments share an obvious and important disadvantage: they cannot partition the level of infection reduction to the individual control methods. Disentangling the efficacies of the different controls when they are used in conjunction is impossible, as is the precise estimation of any synergistic effect between controls. This presents strong motivation for capitalizing upon biologically realistic simulation modeling to inform optimal *C. difficile* control combinations.

Combinations of control for reducing pathogen colonization

Figure 3 shows the combined effect of the four simulated control methods in reducing the ratio of *C. difficile* colonized patients discharged relative to those admitted. All control methods generated marked improvements in reducing the colonized ratio. However, probiotics/bacteriotherapy were less effective than antimicrobial stewardship, reductions in transmission and LoS. Antimicrobial stewardship levels resulting in a halved proportion in the vulnerable epidemiological categories reduced the colonized ratio by a half and it improved the reduction achieved by all other control methods. For example, the maximum reduction in the colonized ratio achieved in combination with probiotics/bacteriotherapy (i.e., through halving the proportion on broad-spectrum antimicrobials from 50% to 25%, while expediting gut flora recovery from 90 days to 10 days) was two-thirds compared to the reduction by a factor of one-third achievable with probiotics/bacteriotherapy alone.

All combinations of other methods with reduced transmission coefficient yielded parameter spaces in which the numbers of colonized patients admitted to hospital exceeded those discharged (a colonized ratio of less than 1). Interestingly, in the (highly idealized) absence of within-hospital transmission, simulations showed that extended

Table 2 Summary of the clinical studies examining the efficacy of control bundles in mitigating *Clostridium difficile* infection

Study	*C. difficile* strain	Study population (*n*)	Control bundle details	Effect size
Bishop *et al*., 2013[53]	Endemic strain unreported	Surgical inpatients (17, 145)	Resident rounding; hand hygiene; maintaining gastric acidity; antimicrobial stewardship	From 2.8/1000 to 1.8/1000 pd[a]
Koll *et al*., 2013[52]	Endemic strain unreported	Acute care inpatients >18 years across 35 hospitals (14, 591 CDI cases)	Contact precaution; hand hygiene; isolation; environmental cleaning	From ~12/10 000 to ~8/10 000 (hosp bed days)
Abbett *et al*., 2009[50]	Endemic strain unreported	Acute care inpatients >18 years (881 CDI cases)	Contact precaution; hand hygiene; environmental cleaning; vancomycin	From 1.1/1000 to 0.66/1000 pd
Salgado *et al*., 2009[51]	Epidemic strain unreported	Tertiary care inpatients >18 years (610 beds, 6 years)	Contact precaution; environmental cleaning; hand hygiene	From 1.8/1000 immediately post-epidemic to 1.2/1000 pd, 3 years thereafter
Weiss *et al*., 2009[49]	Epidemic (NAP1/027)	Acute care inpatients (554 beds, 5 years)	Environmental cleaning; contact isolation; antimicrobial stewardship	From 37.3/1000 to 14.5/1000 (admissions)
Muto *et al*., 2007[48]	Epidemic (NAP1/027)	Tertiary care inpatients (834 beds, 8 years)	Environmental cleaning; hand hygiene; contact isolation; antimicrobial stewardship	From 7.2/1000 to 3.0/1000 (hospital discharges)

[a] pd, patient days.

length of stay was actually beneficial in reducing the colonized ratio. This is because no patients are newly exposed to the pathogen in this idealized (theoretical) setting, combined with the fact that some colonized patients lose carriage of *C. difficile* during their stay in hospital.

Combinations of control for reducing disease incidence

In the absence of additional infection control ('additional' because hospitals are never in a state of no-control) the incidence of disease is 2.8 per 1000 hospital bed days (SD: 4.2). This lies towards the top of the range described in the most comprehensive survey which was carried out in Europe,[54] accounting for the high rates of underreporting associated with milder, symptomatic infection.[39] Figure 4 shows the simulated reduction in CDI incidence in hospital inpatients (per 1000 hospital bed days) as a result of the different combinations of control methods. The surfaces are more jagged because of the increased influence of stochastic effects in the smaller sub-population in diseased (versus colonized) categories.

Antimicrobial stewardship yielded meager benefits in terms of reducing the incidence of CDI, regardless of combination with other methods. Likewise, prescribing probiotics/bacteriotherapy in order to expedite gut microbiota recovery were ineffective control tools and combining them with other transmission reduction methods failed to yield any synergistic effect.

Reducing the transmission coefficient (β) through improvements to hygiene and sanitation had a comparatively large effect in decreasing the incidence of disease. However, even complete elimination of

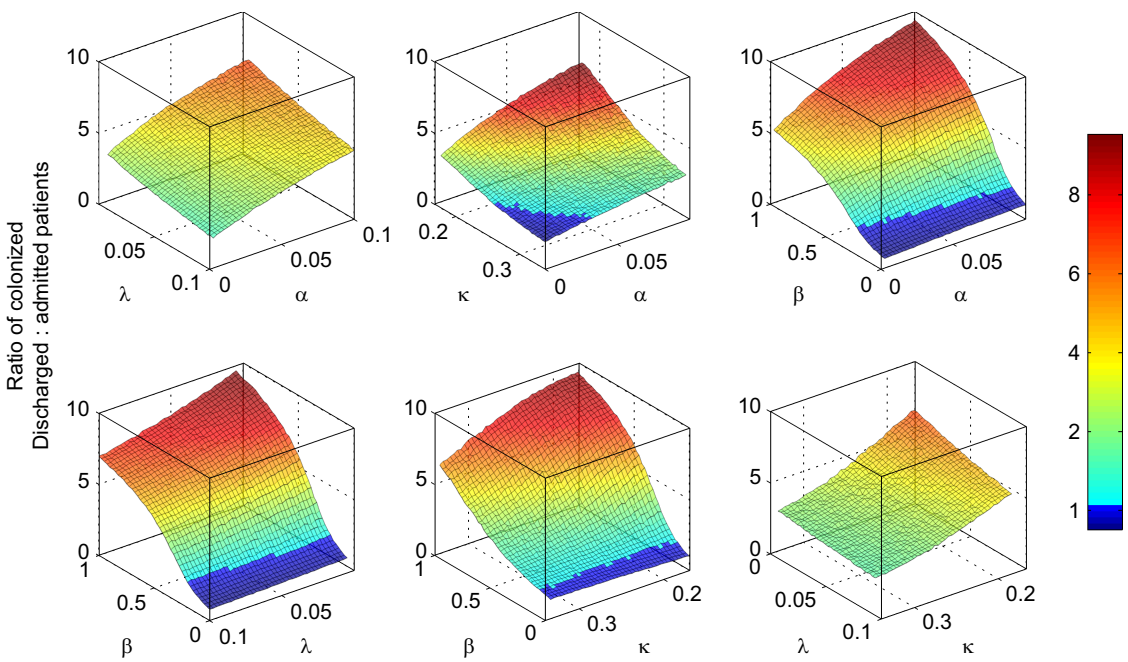

Figure 3 The effect of control combinations on the ratio of patients discharged relative to those admitted with asymptomatic *C. difficile* colonization. Controls include: λ, rate of gut microbiota recovery which is expedited by probiotics or intestinal microbiota transplantation; α, rate of antimicrobial prescription which is reduced through stricter stewardship; β, the rate of transmission which is reduced through improvements to hygiene and sanitation; κ, the rate of patient discharge (inverse of average length of stay), which is increased to minimize patient exposure window.

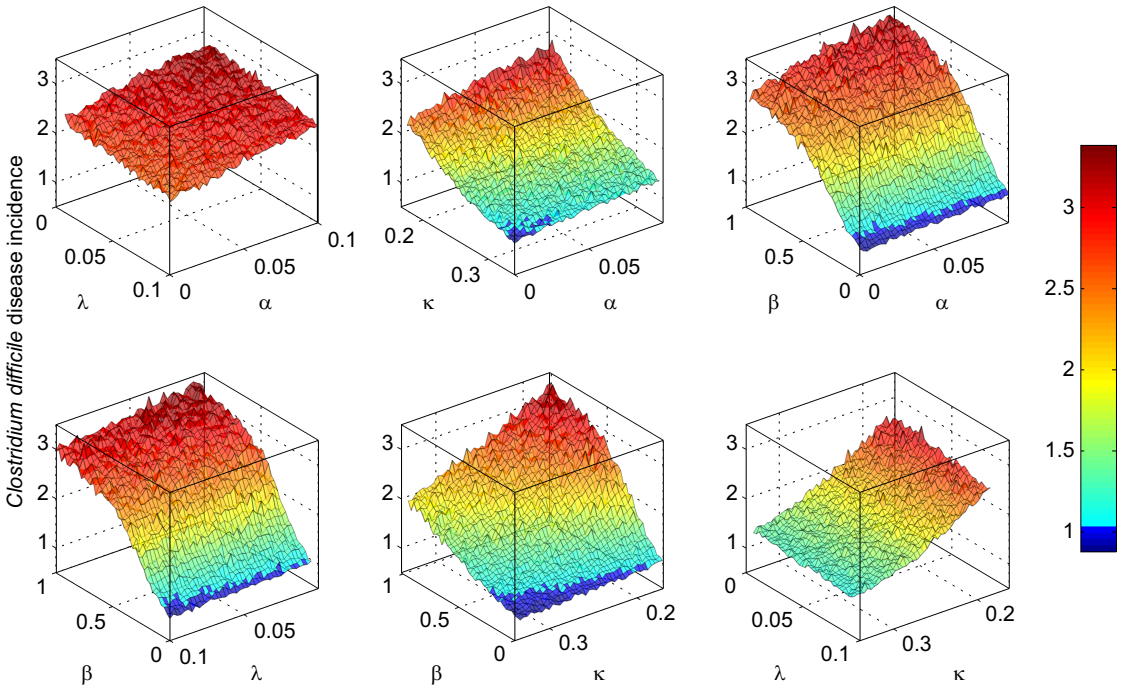

Figure 4 The effect of control combinations on *C. difficile* symptomatic disease incidence per 1000 hospital bed days. Controls include: λ, rate of gut microbiota recovery which is expedited by probiotics or intestinal microbiota transplantation; α, rate of antimicrobial prescription which is reduced through stricter stewardship; β, the rate of transmission which is reduced through improvements to hygiene and sanitation; κ, the rate of patient discharge (inverse of average length of stay) which is increased to minimize patient exposure window.

within-hospital transmission fails to completely eliminate the incidence of CDI because patients who are already exposed or colonized will still import the infection when admitted. Combining this method with either antimicrobial stewardship or prescription of probiotics/bacteriotherapy yielded little additional benefit compared with transmission reduction alone (with marginal improvement attained by combination with antimicrobial stewardship). Reducing the average length of stay (κ^{-1}) was also effective in decreasing disease incidence. Although probiotics/bacteriotherapy did not improve upon control based on LoS reduction, simulations indicated a small benefit in combining LoS reduction with antimicrobial stewardship. The only combination of methods that provided significant gains in ameliorating CDI incidence was the simultaneous reduction in LoS and the transmission coefficient. When both of these parameters were set to the minimum values (maximum control level includes eliminating within-ward transmission, $\beta=0$, by improving sanitation and reducing average length of stay from 6 days to 3 days), the resulting incidence in CDI for hospital inpatients was reduced by two-thirds: from 2.8 (SD: 4.2) to 0.9 per 1000 hospital bed days (SD: 1.5).

DISCUSSION

Mathematical model development offers a framework for safely assessing the efficacies of available infection control methods through simulation and scenario analysis. To date, models of *C. difficile* transmission are sparse and most are very simplistic, omitting factors that are known to be crucial to the epidemiology of this globally relevant disease. Such factors include the possibility of colonization and disease in individuals who have not recently taken antimicrobials—an alarming characteristic that has recently received a great deal of attention.[13,28] Here, we have presented a biologically realistic model of *C. difficile*; used it to simulate the modern epidemiology of the pathogen; and, analyzed control combinations in order to strategize a more integrated approach to control.

We have shown that more stringent antimicrobial stewardship and the prescription of probiotics/bacteriotherapy are both ineffective at reducing symptomatic disease incidence, either in isolation or combination with each other or the other simulated control methods. Although evidence for the benefits reported from administering probiotics/bacteriotherapy is variable,[47,55,56] recent studies have unanimously suggested antimicrobial stewardship to be an effective method of reducing the rate of CDI in hospitals.[57–60] However, attributing the level of infection reduction from this particular control method alone is not yet possible because these studies describe stewardship in conjunction with (often unspecified) additional infection control procedures.[59,60]

A recent hospital-based study from the UK surveyed the bacterial isolates from 1223 cases of symptomatic *C. difficile* infection.[61] From analyzing whole-genome sequence similarity (two or fewer single nucleotide variants), these researchers inferred that 35% of patients with *C. difficile* infection had been infected by other patients (the remaining 65% having been infected outside of the Oxford-based hospital). Our simulation output agrees in that it also demonstrates an inability to eliminate *C. difficile* from the hospital simply through cessation of within-hospital transmission. However, simulations indicate that under this highly idealized scenario of no within-hospital transmission, closer to 60% of infections can be controlled (Figure 4). This qualitatively similar but quantitatively distinct result requires further investigation. One plausible explanation could be that new infections originating from patients with milder symptoms may have been missed in the Oxford study due to the under-reporting of disease that is known to occur for milder *C. difficile* infection.[37,62]

In addition to the benefits in transmission reduction achieved with improvements to sanitation and hygiene, simulations demonstrate the very substantial infection control achieved with reducing the average LoS. Moreover, the combined benefit of reducing LoS and improving sanitation and hygiene significantly exceeds that achieved with either method alone. In other words, adopting a strategy combining both tools will reduce the extent to which either would otherwise be required in isolation to achieve the same gains in CDI reduction.

In terms of the ratio of colonized patients discharged relative to those admitted, all control methods performed well. Antimicrobial stewardship showed greater efficacy in colonization control than it did for disease control, resulting in a maximum reduction of around 50%. Additionally, combining antimicrobial stewardship (halving the proportion of inpatients in the vulnerable epidemiological categories) with probiotic/bacteriotherapy prescription (expediting gut recovery from 90 to 10 days) reduced the colonized ratio by up to two-thirds. Improved sanitation and hygiene and reduced LoS provided notable reductions in the colonized ratio and each was complemented with the addition of any of the other control tools.

As with other infection models, the transmission coefficient is critical to the disease's epidemiology. The transmission coefficient in this healthcare setting, as is the case for all infectious disease models, is difficult to define according to the numerous behavioral elements entailed. An important limitation in the current study is that infection was only simulated to pass between inpatients (or, at least, infection occurred at a level that was proportional to the prevalence of infectious patients). In reality, hospital staff and patient visitors will also act as infection sources and reservoirs. Partitioning the relative contribution of these (and other) separate sources of infection can easily be achieved in a modeling framework, but parameterization will be impossible until the molecular epidemiology of this disease is better described. Rubin *et al.*[18] recently made some progress to this end by using an agent-based modeling approach for simulating combinations of controls (isolation, hand hygiene, environmental cleaning) across a complex contact network of individuals within a hospital. Despite a very simplified epidemiological description of *C. difficile* (individuals were either susceptible, asymptomatically infected or symptomatically infected), simulation output qualitatively matched our own: environmental cleaning/hand hygiene was very effective at reducing within-hospital transmission.

A further limitation of our study is our inability to simulate a given strain in a given setting. Instead, we have had to source the parameterization of our model across multiple settings (and multiple strains). No single study presents all the required parameter values for our model. Understandably, this is a common issue among biologically realistic simulation models.[42] Importantly, in the event of a thorough epidemiological analysis of a particular strain of *C. difficile* whereby complete (or, at least, near-complete) model parameterization will be made possible, we have a functional and biologically realistic model that will provide a valuable contribution to future outbreak analysis. The next phase of development for this research is the conversion of the general, strategic framework presented here into a more tactical (idiosyncratic) tool for exploring control options for CDI in a specified healthcare setting. This requires location-specific data collection to inform model parameterization (e.g., pre-intervention rates of infection and colonization; local antimicrobial prescribing behaviors; the average length of stay for a particular hospital and the feasible level to which this can be reduced, *etc.*).

Despite advances in other infectious disease epidemiology settings,[63–66] research into strategic infection control combinations for healthcare-acquired pathogens is underdeveloped. By reviewing the literature on control bundles for reducing *C. difficile* transmission and presenting simulation results for what we consider to be the most biologically realistic model of *C. difficile* reported to date, we hope to have provided important contributions to this burgeoning field. Whether our conclusions translate to other relevant epidemiological settings, such as long-term care facilities,[67] requires further investigation. Given the similarities between *C. difficile* and other important healthcare acquired infections (e.g., methicillin-resistant *Staphylococcus aureus*), the framework that we present here should be easily adaptable to other pathogens in future studies.

ACKNOWLEDGMENTS

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