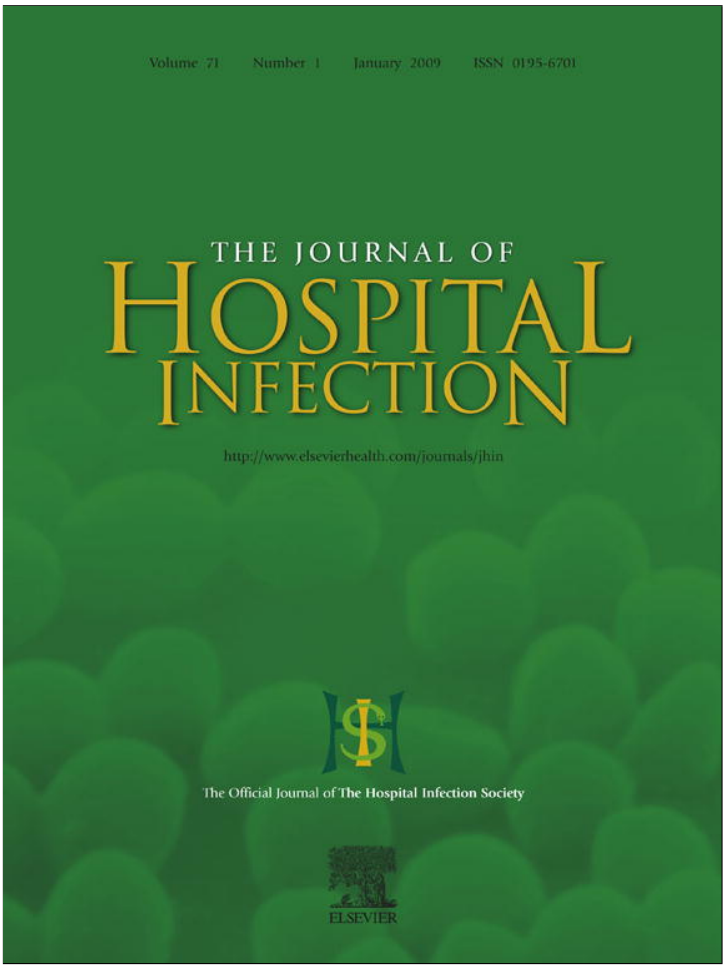

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Spatio-temporal stochastic modelling of *Clostridium difficile*

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Summary *Clostridium difficile*-associated diarrhoea (CDAD) occurs sporadically or in small discrete outbreaks. Stochastic models may help to inform hospital infection control strategies. Bayesian framework using data augmentation and Markov chain Monte Carlo methods were applied to a spatio-temporal model of CDAD. Model simulations were validated against 17 months of observed data from two 30-bedded medical wards for the elderly. Simulating the halving of transmission rates of *C. difficile* from other patients and the environment reduced CDAD cases by 15%. Doubling the rate at which patients become susceptible increased predicted CDAD incidence by 63%. By contrast, doubling environmental load made hardly any difference, increasing CDAD incidence by only 3%. Simulation of different interventions indicates that for the same effect size, reducing patient susceptibility to infection is more effective in reducing the number of CDAD cases than lowering transmission rates.

Introduction

Clostridium difficile-associated diarrhoea (CDAD) is a common hospital-acquired infection causing considerable morbidity and mortality.[1] To date, hospital infection control policies have made little impact on incidence.[2] Epidemiological data about CDAD are key to devising effective infection control policies. Unfortunately, the epidemiology of

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CDAD in hospitals is complex because cases mostly occur sporadically or in small outbreaks in any particular location at any particular time. Epidemiological approaches that can address the stochastic nature of CDAD are therefore essential.[3] Moreover, the likelihood that an index case will give rise to an outbreak of CDAD, which depends on the susceptibility of at-risk patients, also needs consideration.[4] Unlike the states of colonisation and toxin production, the state of susceptibility to colonisation cannot be observed directly or reliably quantified from any predictors.[3] Nevertheless, risk factors for colonisation, such as antibiotic use, are suggestive of the kinds of patients who might be considered susceptible to CDAD. Epidemiological models of CDAD can take such risk factors into account when making inferences about the state of susceptibility of any individual patient. Simple stochastic models of colonised and infected states have been successfully applied to meticillin-resistant *Staphylococcus aureus* infections in intensive care units.[5]

Producing a stochastic spatio-temporal model of CDAD is not enough in itself. Such a model should perform in a way that closely mirrors observed data from settings that would be typical of areas where CDAD occurs within hospitals. This can be aided by drawing on known data, such as patient admission rates, to provide parameter estimates for the model rather than choosing arbitrary starting values for the simulation. Moreover, having produced a realistic model, it should be open to a range of manipulations that suggest the likely consequences when different types of hospital infection-control policies are employed. We collected extensive environmental and stool sample data from two 30-bedded medical wards for the elderly and typed the strains according to the molecular mass of their S-layer proteins, to provide a reference standard against which the model could be compared.[6,7]

Methods

Observed data

The data, described in detail elsewhere, comprise 1003 faecal specimens from 390 patients (mean age: 82.5 years; range: 65—101) admitted to two hospital wards over a 17 month period following written consent with the approval of the local research ethics committee.[6] A total of 290 patients were *C. difficile* culture negative and 100 culture positive, 34 of whom were toxin positive. The layout of the two wards was identical, with four six-bedded bays and six single rooms each. Environmental samples ($N = 1348$) were also obtained from the two wards over the same period, of which 185 (13.7%) were culture positive.[7] Of the faecal and environmental isolates 73% and 91%, respectively, were identified as the single epidemic strain prevalent at the time in the UK.[7]

Epidemiological model

The proposed model is constructed using standard stochastic modelling techniques based on the following assumptions regarding the biology of *C. difficile* infection. Under normal circumstances individuals are immune from colonisation by *C. difficile*, but may become susceptible due to factors such as treatment by antibiotics. If colonised, a patient may develop clinical symptoms of diarrhoea following toxin production. It is proposed that colonised (and toxin-positive) patients present a source of infection to susceptible patients in addition to potential environmental sources of infection.

Based on these assumptions, the patient population in the ward is partitioned into the following classes: immune (R, R_1), susceptible-uncolonised (SU), susceptible-colonised (SC) and toxin positive (TP). The classes R and R_1 represent those patients who are resistant to infection to whom immunity might be conferred not only by humoral and cellular responses, but also by bacterial interference and other mechanisms. The immune classes R and R_1 respectively denote those immune individuals who are not receiving antibiotics and those who are receiving antibiotics. We assume that individuals in R and R_1 pass to the susceptible class (S) after a random time following an $\exp(\lambda_1)$ [$\exp(\lambda_{1a})$, $\exp(\lambda_{1b})$ respectively] distribution.

Patients in SU become colonised through a combination of three processes in the model. Colonisation can be due to contact with: a class SC or TP patient in the same room; a colonised (class C) or TP patient in a different room; or, from 'environmental' sources independent of the status of other patients in the ward representing background levels not attributable to any individual patient. We therefore take account of which room patients occupy and assume that patients within the same room mix homogeneously with each other. The probability that an individual in class *SU* at time t becomes colonised in a short time period $(t,\ t + \mathrm{d}t)$ is given by

$$\Phi(t) = (\epsilon + \beta_1 n_s(t) + \beta_2 n_d(t))\mathrm{d}t + \mathrm{o}(\mathrm{d}t),$$

where $n_s(t)$ and $n_d(t)$ denote (for a given individual) the numbers of SC and TP patients in the same room and in different rooms, respectively,

and ϵ denotes the rate of colonisation from the environment. The parameter β_1 represents the rate at which a patient in class SC or TP has an infectious contact with a patient in the same room, while β_2 represents this rate for patients in different rooms. Since it is believed that contact between patients occurs inter alia as a result of toilet-sharing and nursing practices, we should anticipate that β_1 should exceed β_2 for the *C. difficile* system. Once patients enter the SC state, it is assumed that they remain there for a period of time given by an exp(μ) distribution, before proceeding to the TP state. Once patients are TP, then they are given antibiotic treatment for the condition. In the model it is assumed that such patients revert to being susceptible after a random time drawn from an exp(γ) distribution.

To represent the processes of patient admission and discharge in the model, we assume that patients are presented to the ward as a Poisson process with rate α and are admitted if there is at least one empty bed on the ward. We also include parameters describing the probabilities of admission into each compartment (R, R_1, SU, SC and TP). The discharge of patients is represented as a random process, and the probability that a given patient in class X is discharged in the interval (t, $t + \mathrm{d}t$) is given by $\rho_X \mathrm{d}t$. The parameters are defined and described in Table I, and a schematic representation of the model structure is given in Figure 1. For parameters estimated by Markov chain Monte Carlo (MCMC), the estimates are the modal values of the posterior marginal distributions. Credible intervals (equal-tailed) are obtained for parameters estimated from MCMC by taking lower and upper quartiles of the simulated distributions. In Figure 1 rates at which transitions occur between compartments are denoted by the parameters assigned to each arrow in the diagram. The proportions of arrivals that enter R_1, *SC* and *TP* are given by q_1, q_2 and q_3, respectively, with remaining arrivals entering *R*.

Parameter estimation

The parameters in the above model are estimated within a Bayesian framework using data augmentation and MCMC methods. The use of these techniques to analyse epidemic data of this form is now widespread.[5,8,9] Their main advantage lies in their ability to analyse data from partially observed processes by treating unobserved information as additional unknown parameters in the model. In summary, let $\boldsymbol{y}$ denote the observed information (derived from ward admission/discharged information, stool samples and observed incidence of cases of *C. difficile*), $\boldsymbol{\theta}$ denote the vector of model parameters as defined in Table I, and $\boldsymbol{x}$ denote the vector of transition times between compartments for all patients present in the ward during the study time. The computational Bayesian approach operates by first assigning a prior probability density to $\boldsymbol{\theta}$, $\pi(\boldsymbol{\theta})$, to represent our belief regarding the model parameters. In this study we assume little prior knowledge of parameters and assume that a priori all parameters have independent uniform distributions over

Table I Parameters used in baseline simulations for the model in Figure 1

Symbol	Description/transition rate	Estimate	95% credible interval/ confidence interval	MCMC/MLE
α	Overall arrival rate	1.3	(1.204, 1.403)	MLE
λ_1	$R \rightarrow SU$	0.012	(0.008096, 0.01670)	MCMC
λ_{1a}	$R_1 \rightarrow SU$	0.013	(0.007781, 0.01988)	MCMC
ϵ	$SU \rightarrow SC$ (colonisation due to backround environmental contamination)	0.019	(0.008085, 0.04533)	MCMC
β_1	$SU \rightarrow SC$ (colonisation due to within-room transmission)	0.185	(0.08854, 0.3293)	MCMC
β_2	$SU \rightarrow SC$ (colonisation due to between-room transmission)	0.0045	(0.0008440, 0.01056)	MCMC
μ	$SC \rightarrow TP$	0.0093	(0.006252, 0.01371)	MCMC
γ	$TP \rightarrow SU$	0.4603	(0.3205, 0.6595)	MLE
ρ_1	Exit rate from *R*	0.033	(0.02826, 0.03816)	MCMC
ρ_{1a}	Exit rate from R_1	0.033	(0.02691, 0.03964)	MCMC
ρ_2	Exit rate from *SU*	0.008	(0.002561, 0.01876)	MCMC
ρ_3	Exit rate from *SC*	0.036	(0.02717, 0.04649)	MCMC
q_1	Proportion of R_1 arrivals	0.1637	(0.1308, 0.1966)	MLE
q_2	Proportion of *SC* arrivals	0.00197	(0.00004, 0.0011)	MLE
q_3	Proportion of *TP* arrivals	0.00197	(0.0004, 0.0011)	MLE

Rates are derived either by maximum likelihood estimation (MLE) or by Markov chain Monte Carlo (MCMC) methods.

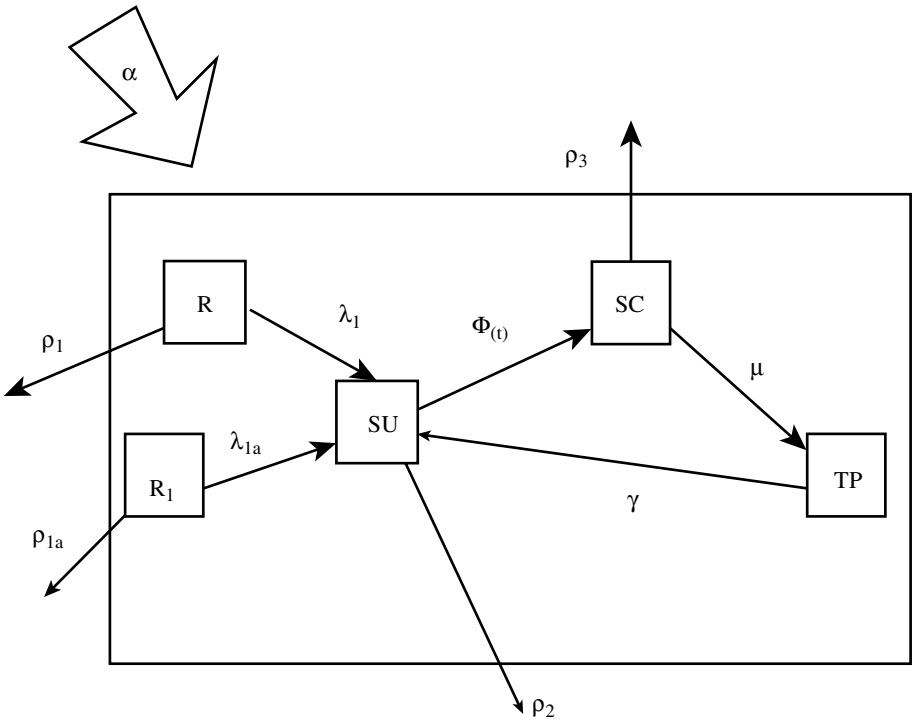

Figure 1 Schematic diagram of stochastic compartment model for *C. difficile* dynamics in a hospital ward. Note that the arrival process allows for arrival into several different states (*R*, R_1, *SC*, and *TP*), but for simplicity these are not all represented in the diagram.

the interval between 0 and 1, so that $\pi(\boldsymbol{\theta})$ is constant over a wide range of plausible parameter values. This is then updated in the light of the data $\boldsymbol{y}$ by drawing samples $\{(\boldsymbol{\theta}, \boldsymbol{x})\}$ from the joint posterior distribution $\pi(\boldsymbol{\theta}, \boldsymbol{x}|\boldsymbol{y})$. The model parameters, $\boldsymbol{\theta}$, can then be estimated from their marginal distributions $\pi(\boldsymbol{\theta}|\boldsymbol{y})$. The algorithm used to sample from $\pi(\boldsymbol{\theta}, \boldsymbol{x}|\boldsymbol{y})$ involves constructing and simulating from a Markov chain whose equilibrium distribution is $\pi(\boldsymbol{\theta}, \boldsymbol{x}|\boldsymbol{y})$, using standard Metropolis—Hastings techniques to update model parameters and patient transition times during the simulation. In summary, we are using the standard Bayesian approach to update our prior beliefs regarding the parameters $\boldsymbol{\theta}$, represented by the distribution $\pi(\boldsymbol{\theta})$, in the light of the data $\boldsymbol{y}$, to give a posterior distribution $\pi(\boldsymbol{\theta}|\boldsymbol{y})$. For further explanation, introductory texts on stochastic compartmental modelling, including Bayesian computational methods, are recommended.[10]

In this study we do not apply Bayesian methods in the estimation of all 15 parameters defined in Table I. For it is possible to estimate certain parameters, governing transitions for which the data give complete information (e.g. arrival rates), directly using maximum likelihood. These are then 'fixed' at the estimated values and the remaining parameters are estimated using MCMC by setting them to their posterior modal value.

Results

Table I lists the estimated values for parameters together with the method of estimation (maximum likelihood or MCMC). These estimated values are used as baseline values for a sensitivity study of how *C. difficile* dynamics may be influenced by control strategies. It should be noted that the credible intervals (Bayesian equivalent of confidence intervals) for these parameters are typically very wide so that the point estimates provided should not be regarded as precise estimates.

Observed and simulated data

We first consider how well the model parameterised using the values in Table I can reproduce qualitatively the incidence of TP cases observed in the study. Figure 2(a) shows the daily incidence of TP cases in the study ward over the two years of the study. The stochastic simulations in (b) and (c) illustrate the variability to be expected in the degree of clustering over a one-year interval.

Effects of changing model parameters

An important application of the model is to assess the potential impact of control strategies on the

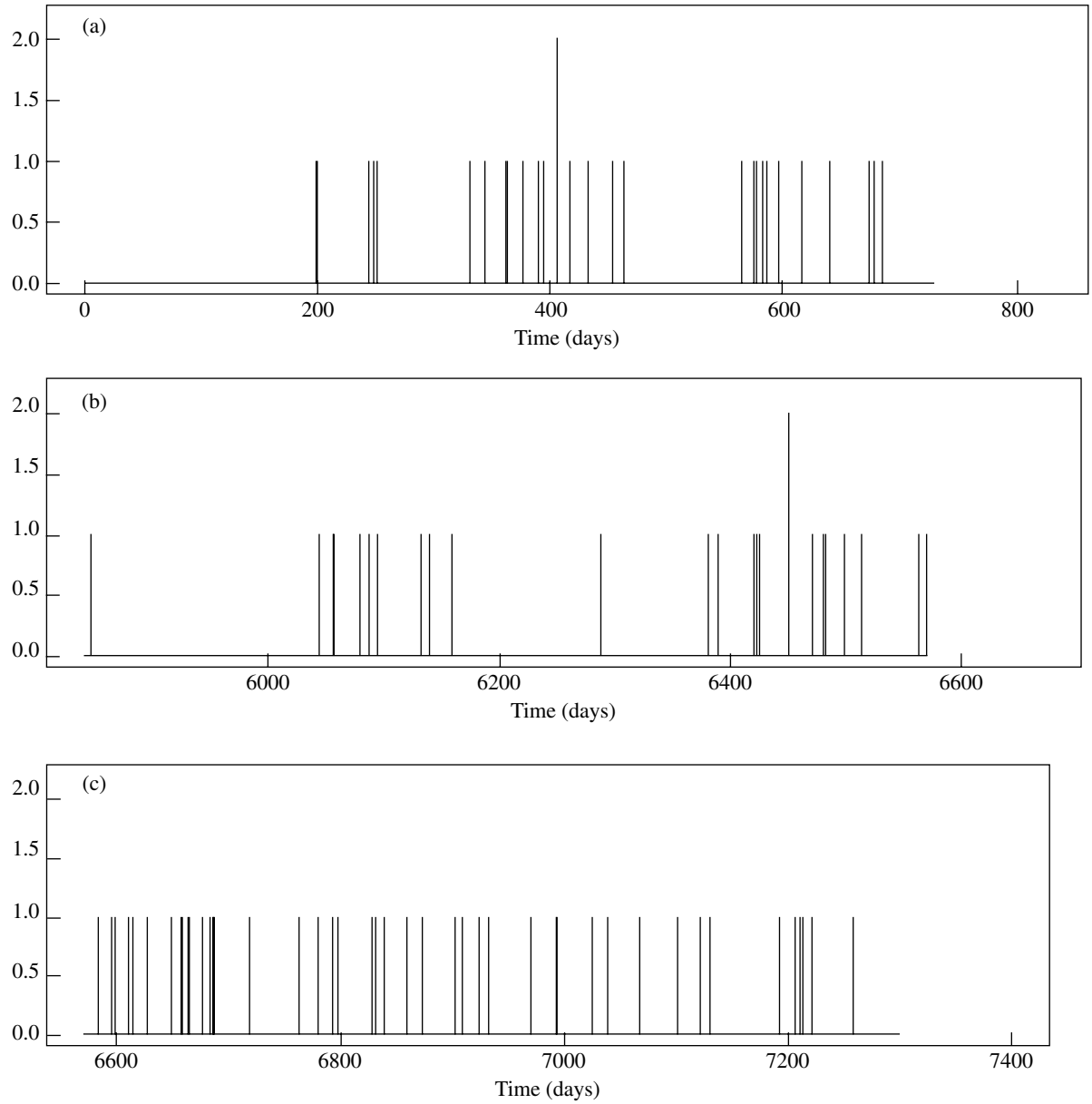

Figure 2 Temporal incidence of toxin-positive cases: (a) in data from study; (b) and (c) from simulations in an identical ward with the stochastic model parameterised using values of Table I. The lower pair of graphs represent incidence in years 17 and 18 (b) and 19 and 20 (c) from a 20 year simulation.

incidence of toxin-positive cases. We consider a range of distinct scenarios in which key parameters from Table I governing the colonisation process (ϵ, β_1 and β_2) and the transition rates to the SC class (λ_1, λ_{1a}) are increased or decreased from their baseline values [scenario (a)] by a factor of 2. The simulation scenarios (a)—(m) in Table II and Figure 3 are generated by scaling the five parameters (λ_1, λ_{1a}, ϵ, β_1, β_2) with respect to their baseline values given in Table I investigated in terms of the mean number of toxin-positive cases per annum, estimated from 100 independent 20-year simulations for each scenario. A 95% confidence interval for the annual mean is also given for each scenario in Table II.

Discussion

Over the 18 months of observation, CDAD occurred sporadically as one or two cases in any particular place at any particular time. There was the equivalent of 350 cases per 1000 bed-years on the unit. With the UK National Health Service (NHS) having ~150 000 beds, if a similar pattern occurred throughout the NHS, this would equate to a predicted 52 500 CDAD cases per year

Table II Estimated expected numbers of toxin-positive (TP) cases per annum for simulation scenarios

Scenario and scaling factors for (λ_1, λ_{1a}, ϵ, β_1, β_2)	TP cases per year	95% confidence interval	Relative to (a)
(a) (1, 1, 1, 1, 1)	21.19	(20.96, 21.43)	1.0
(b) (0.5, 0.5, 0.5, 0.5, 0.5)	9.81	(9.64, 9.97)	0.46
(c) (2, 2, 2, 2, 2)	36.32	(36.0, 36.63)	1.73
(d) (1, 1, 0.5, 0.5, 0.5)	18.09	(17.88, 18.29)	0.85
(e) (1, 1, 2, 2, 2)	22.55	(22.33, 22.78)	1.06
(f) (1, 1, 0.5, 2, 2)	20.30	(20.07, 20.53)	0.95
(g) (1, 1, 1, 0.5, 0.5)	19.37	(19.17, 19.58)	0.91
(h) (0.5, 0.5, 1, 1, 1)	12.03	(11.87, 12.19)	0.57
(i) (1, 1, 2, 1, 1)	21.83	(21.58, 22.10)	1.03
(j) (1, 1, 1, 2, 2)	22.34	(22.11, 22.56)	1.05
(k) (2, 2, 1, 1, 1)	34.33	(34.07, 34.61)	1.62
(l) (1, 1, 1, 0.5, 1)	20.48	(20.26, 20.71)	0.97
(m) (1, 1, 1, 2, 1)	21.67	(21.44, 21.91)	1.03

The estimates are based on 100 independent 20-year simulations; 95% confidence interval (CI) is given along with the point estimate. Simulation (a) represents the baseline scenario (Table I), corresponding to a vector of scaling factors (1, 1, 1, 1, 1) applied to (λ_1, λ_{1a}, ϵ, β_1, β_2). For the other scenarios the corresponding scaling factors are:
(b) halving all rates of becoming susceptible and *C. difficile* transmission (0.5, 0.5, 0.5, 0.5, 0.5),
(c) doubling all rates of becoming susceptible and transmission (2, 2, 2, 2, 2),
(d) halving all transmission rates (1, 1, 0.5, 0.5, 0.5),
(e) doubling all transmission rates (1, 1, 2, 2, 2),
(f) halving transmission rate from background environmental contamination, but doubling rates due to direct or indirect transmission from other patients (1, 1, 0.5, 2, 2),
(g) halving transmission rates from other patients (1, 1, 1, 0.5, 0.5),
(h) halving rates of patients becoming susceptible (0.5, 0.5, 1, 1, 1),
(i) doubling transmission rate due to background environmental contamination (1, 1, 2, 1, 1),
(j) doubling transmission rates from other patients (1, 1, 1, 2, 2),
(k) doubling rates of patients becoming susceptible (2, 2, 1, 1, 1),
(l) halving transmission rate from patients within the same room (1, 1, 1, 0.5, 1),
(m) doubling transmission rate from patients within the same room (1, 1, 1, 2, 1).

in the UK.[2] There were 51 690 CDAD cases in the UK in 2005, so the data are likely to be reasonably representative of the current situation, though they would have been relatively high for the actual observation period of 1999—2001.[2] This might be expected given the selected case-mix of patients aged $\geq$65 years. Our stochastic spatio-temporal model produces patterns of colonisation and CDAD that closely resemble the observed data. Manipulating model parameters is thus likely to indicate the consequences of different hospital infection control strategies fairly reliably. Halving the rate that patients become susceptible has the greatest effect on the number of CDAD cases, reducing it by 43%. Doubling the rate of becoming susceptible increases predicted CDAD incidence by 62%. By contrast, manipulation of environmental *C. difficile* load is the least effective strategy. Doubling environmental load makes a relatively slight difference, increasing CDAD incidence by only 3%. Halving colonisation derived from other patients has a similarly sized effect of reducing CDAD incidence by 9%; doubling patient-derived colonisation increases incidence by 5%. Halving colonisation from any source reduces CDAD incidence by 15%. Notably, doubling colonisation rate derived from patients within the same bay only increases incidence by 3%, with the implication that susceptible patients are at greater risk from the larger number of patients not in the same bay than those to whom they are in close proximity. Note that these percentages are subject to a degree of uncertainty as indicated by the confidence intervals for the expected rates indicated in Table II. While the results suggest that an intervention reducing transition rates to the SU class by 50% will be more beneficial than one which achieves a proportionately similar reduction in colonisation rates, it is clear that the degree of reduction that is practically feasible will depend on the parameter concerned. In assessing infection control strategies the likely effect size of any intervention needs to be considered.

The model's prediction that reducing patient susceptibility is the most effective CDAD hospital infection control strategy is consistent with the observed impact of antibiotic prescribing, especially reducing intravenous cephalosporin use.[11] Effect sizes similar to those predicted have been

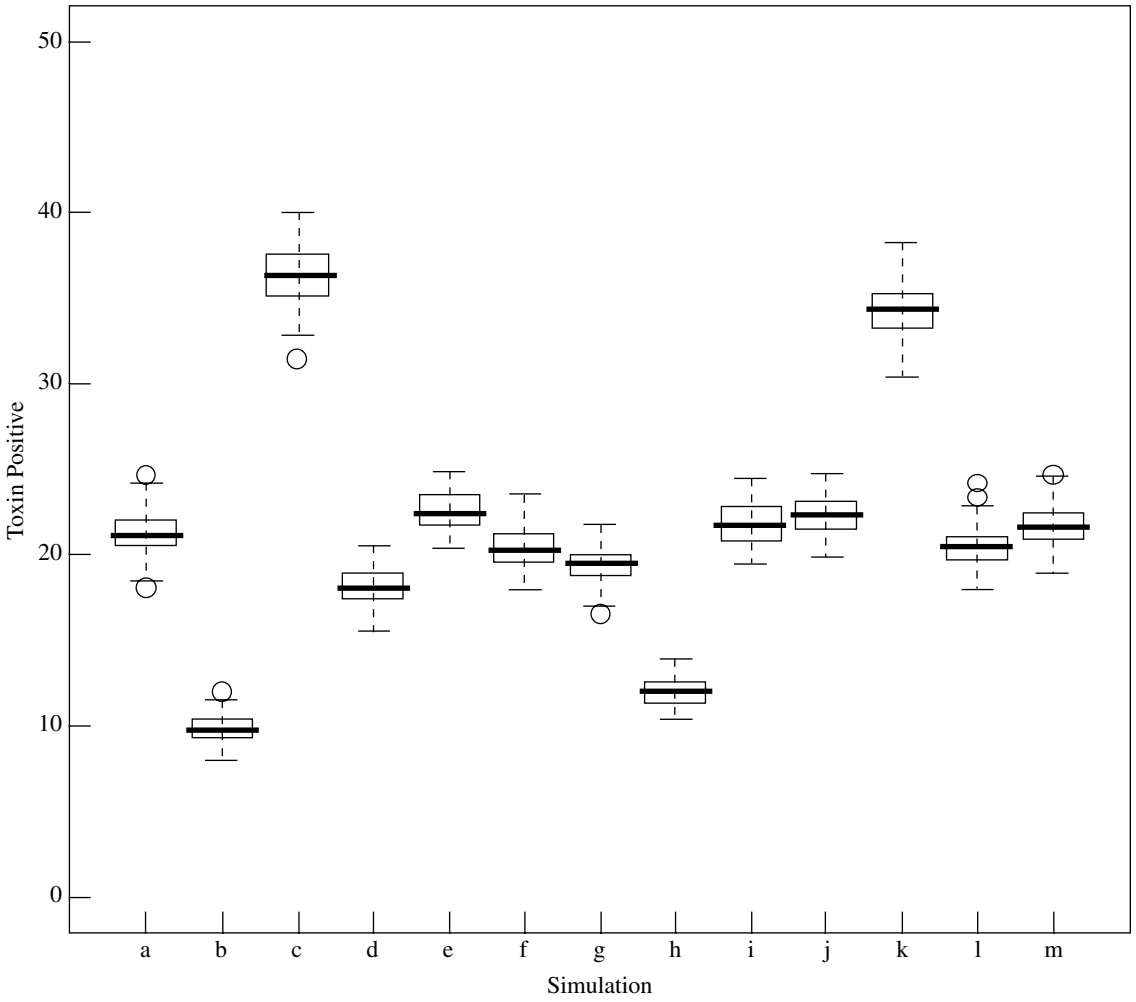

Figure 3 Box plots of average numbers of toxin-positive cases per year for simulation scenarios. For each simulation scenario the plot is obtained from 100 independent 20-year simulations.

observed in randomised controlled trials of probiotics to prevent CDAD, though the small number of cases means that such differences often fail to reach significance.[12,13] The lack of studies with sample sizes large enough to be adequately powered emphasises the utility of a modelling approach. This is able to indicate likely effect sizes of potential interventions and thus enable researchers to estimate appropriate trial sample sizes more accurately. There are even less data that inform about the effects of environmental cleaning on CDAD. This is because environmental cleaning is usually part of a broader infection control strategy, but is reported to be less effective than antibiotic prescribing control.[14,15] Wilcox's group investigated the effect of environmental cleaning extensively in a setting with a CDAD incidence similar to that found in this study. They also found that ~90% of environmental contamination is due to the single epidemic strain and thus its source cannot be identified.[16] They showed that cleaning with hypochlorite may reduce CDAD incidence, but pointed out the potential for confounding factors impacting on their results.[17] The predominance of a single strain in the environment also occurred in Samore's study which found that for most *C. difficile* transmission the presumed index case was not responsible.[18] This is in line with the model's prediction that the larger number of patients in other areas of the ward are at least equal in importance for CDAD as those in the immediate environment. However, we had no cases with a hypervirulent strain for which the model may not apply.

One of the limitations of a spatio-temporal model is that it may not apply to situations that differ markedly to the one chosen (e.g. renal transplant units). The CDAD incidence rate we observed appears typical for the UK, but we may have hit a very good or very bad 18 months just by chance, though ongoing informal observations do not suggest this. Moreover, although the model performed well with regard to the observed data,

it relies on several assumptions regarding the stochastic mechanisms that underlie infection dynamics, and the available data are insufficient to allow rigorous model assessment. Nevertheless, the modelling framework is flexible and can be updated in the light of new information; the work described in this paper represents important groundwork for future studies. Moreover, we chose our epidemiological model on grounds of parsimony and biological plausibility in the context of medical wards for the elderly. Other models might be considered and their performance against observed data compared; it may be that for other contexts, such as renal transplant units, alternative epidemiological models might be preferable. An associated limitation is the lack of precision regarding the parameter estimates, again as a result of the scarcity of data to inform a relatively complex model. Therefore, while the baseline parameter estimates are sensible choices around which to base our sensitivity analysis, the large variances in the posterior parameter distributions imply that the 'true' parameters may be somewhat different from those assumed. This should not necessarily invalidate the qualitative findings of the sensitivity analysis.

This is the first study to use the advantages of stochastic spatio-temporal modelling to investigate the epidemiology of CDAD in hospitals. The model fits observed data from a hospital setting with typical features of sporadic CDAD cases. The practical implication for CDAD hospital infection control in the absence of data from adequately powered randomised controlled trials is that for the same effect size, interventions to reduce host susceptibility are superior to those to reduce infectivity either from other patients or the environment. However, it is possible that infectivity interventions can provide far greater effects than those that reduce host susceptibility if it is much easier to reduce infectivity than host susceptibility: relevant empirical data could inform future models.

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Conflict of interest statement
None declared.

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