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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,