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Epidemiological Modelling of *Clostridium Difficile*

Angus McLure
Supervisor: Prof. Geoff Mercer
Australian National University

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Introduction

Clostridium difficile is a species of bacteria which infects the gut causing anywhere from mild diarrhoea to toxic megacolon and death. *Clostridium difficile* infection (CDI) is the most common cause of infectious diarrhoea in hospitalised patients worldwide. Until recently most cases were in elderly patients who had received antibiotics which cleared their native gut flora, allowing the colonisation of *C. difficile* and subsequent development of symptomatic CDI. However more recent studies have shown that children and pregnant women (Benson et al. 2007) are also at risk. Furthermore CDI has been observed to occur in the absence of recent treatment with antimicrobials (Centers for Disease Control and Prevention 2005). There is a rise in incidence and severity of symptoms of CDI worldwide. It is estimated that in the USA alone CDI causes 8,000 deaths (Centers for Disease Control and Prevention 2012) and and costs at least $800 million every year (McGlone et al. 2012).

Very few epidemiological models of CDI have been published. In this paper we consider three models presented by Starr et al. (2009), Lanzas et al. (2011) and Yakob et al. (2013), using the last as a basis for our own model.

Clostridium Difficile

The anaerobic, Gram-positive bacteria *C. difficile* can be found in the intestines of 2-5% of the general population, where for the most part it is harmless. The gut of a healthy individual contains a large community of diverse microorganisms, the gut flora. Most of these microorganisms are harmless and many are beneficial or essential for good health. During a course of treatment involving antimicrobials the gut flora is damaged and must recover. During the recovery period the sparse gut flora allows for the colonisation of new species of bacteria or the expansion of existing antibiotic tolerant species. If these species are pathogenic this may result in (antibiotic associated) diarrhoea (AAD) and psuedomembranous colitis (PMC), either of which may be life threatening. *C. difficile* is the single most common cause of AAD and PMC, being responsible for 30% and 90% percent of cases respectively (Ryan et al. 2010).

Like other clostridia, *C. difficile* may produce a number of toxins. The most commonly studied are toxin A (an enterotoxin) and toxin B (a cytotoxin). It is these toxins which cause the damage to intestinal tissues and diarrhoea when sufficiently large intestinal colonies of *C. difficile* are present, and the detection of these toxins in stool samples is the main diagnostic for CDI (Ryan et al. 2010).

Under conditions of stress *C. difficile* produces spores which are tolerant to a wider range environmental conditions than its vegetative state. In particular the spores can survive long term on most surfaces as they are oxygen tolerant (Ryan et al. 2010). The spores are not killed by alcohol based cleaning agents commonly used in hospitals, and can withstand the acidity of the stomach, allowing transmission between humans via the faecal-oral route (Debast et al. 2013).

Diagnosis, treatment and prevention of CDI

As there are many possible causes of diarrhoea, tests are usually required to diagnose CDI. There is not a consensus on the definitive diagnostic test; however, often a stool sample is tested for the presence of toxin A and/or B (Debast et al. 2013).

Recommended treatment of CDI depends on severity and the number of relapses. For most cases one of the antibiotics Metronidazol, Vancomycin or Fidaxomicin are recommended. If a patient has experienced multiple relapses then transplantation of healthy gut flora is recommended. In severe cases the colon may be surgically removed (Debast et al. 2013).

As prescription of antibiotics seems the be the biggest risk factor for the development of symptomatic CDI, careful antibiotic stewardship appears to be key to managing CDI in hospitals (Debast et al. 2013).

Summary of existing models

In a 2009 paper, Starr et al. put forth a stochastic, spatio-temporal, compartmental model of two identically laid-out wards for the elderly within a single hospital. The

Postal Address: 111 Barry Street
c/- The University of Melbourne
Victoria 3010 Australia

Email: enquiries@amsi.org.au
Phone: +61 3 8344 1777
Fax: +61 3 9349 4106
Web: www.amsi.org.au

notable features of the model are:

1. Only those patients who have been treated with antibiotics are susceptible to C.diff colonisation.

2. Patients may be immune to colonisation with or without having taken antibiotics recently but can lose this immunity.

3. Susceptible patients can become colonised by C.diff. This may be symptomatic (toxin positive), or asymptomatic (toxin negative).

4. The modes of colonisation considered are inter- and intra-ward infection from other colonised patients, and environmental infection. For the former mode the likelihood of infection of a given susceptible individual depends on the number of colonised patients, but for the later the likelihood is independent of the prevalence of C.diff colonisation.

5. The likelihood that a given colonised or diseased patient infects a susceptible patient is dependant on the whether the two are in the same room.

6. Diseased patients can be cured, becoming susceptible (not immune).

7. Patients can be admitted or discharged in any of the states.

Lanzas et al. (2011) developed an ODE model, and derived from it a stochastic model using a combination of the Gillespie direct and first reaction methods. The notable features of the model are:

1. Only those patients who have been treated with antibiotics are susceptible to *C. difficile* colonisation.

2. Only those patients who have normal gut flora are immune to *C. difficile* colonisation. Taking antibiotics is the only mode of the disruption of normal gut flora.

3. Susceptible patients can become asymptomatically colonised. There are two classes of asymptomatically colonised patients, C^+ and C^-. Those patients in the C^+ state mount an effective immune response and so cannot develop symptomatic CDI but do act as a source of infection. Those patients in the C^- class do not mount an effective immune response and so will develop symptomatic CDI.

4. Diseased patients can be cured, becoming susceptible (not immune).

Postal Address: 111 Barry Street
c/- The University of Melbourne
Victoria 3010 Australia

Email: enquiries@amsi.org.au
Phone: +61 3 8344 1777
Fax: +61 3 9349 4106
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5. Patients can be admitted or discharged in any of the states, unless they are susceptible in which case they cannot be admitted but may be discharged.

Yakob et al. (2013) developed their own deterministic ODE model and associated stochastic model. Their model is significantly more complex with seven different states and twenty parameters, but does not consider the effects of having separate wards.

1. No patient is fully immune to *C. difficile* colonisation.

2. Patients can either be susceptible, exposed to but not colonised by *C. difficile* , colonised by *C. difficile* or diseased (toxin positive).

3. In addition, other than diseased (toxin positive) patients, all patients are either considered vulnerable if they have taken antibiotics and thus have depleted gut flora, or not vulnerable if they have normal or recovered gut flora.

4. Slow recovery of gut flora and prescription of antibiotics allow transition between pairs of vulnerable/not vulnerable states.

5. Susceptible patients become exposed upon exposure to colonised and diseased patients, but there is no environmental source of exposure.

6. Exposed patients will eventually become colonised, and colonised patients will eventually become diseased. Colonised and exposed patients cannot revert to a less infected state.

7. Only diseased patients can revert state further back in the progression of the disease. This occurs either due to treatment with antibiotics or self-resolving symptoms. Self-resolved symptoms transition a patient to the vulnerable and colonised state, while treatment transitions either to susceptible and vulnerable or exposed and vulnerable state.

8. Patients can be admitted or discharged in any of the states.

The gross structure of the models are compared in the Figure 1.

Each model has its own shortcomings. The models by Starr et al. and Lanzas et al. both assume that patients who have not taken antibiotics recently have healthy gut flora and simply cannot be colonised by *C. difficile* , which does not agree with recent observations (Centers for Disease Control and Prevention 2005). None of the models allow for recovery from colonisation without development of symptomatic CDI, such as might occur with the administration of antibiotics, a common occurrence in

Postal Address: 111 Barry Street
c/- The University of Melbourne
Victoria 3010 Australia

Email: enquiries@amsi.org.au
Phone: +61 3 8344 1777
Fax: +61 3 9349 4106
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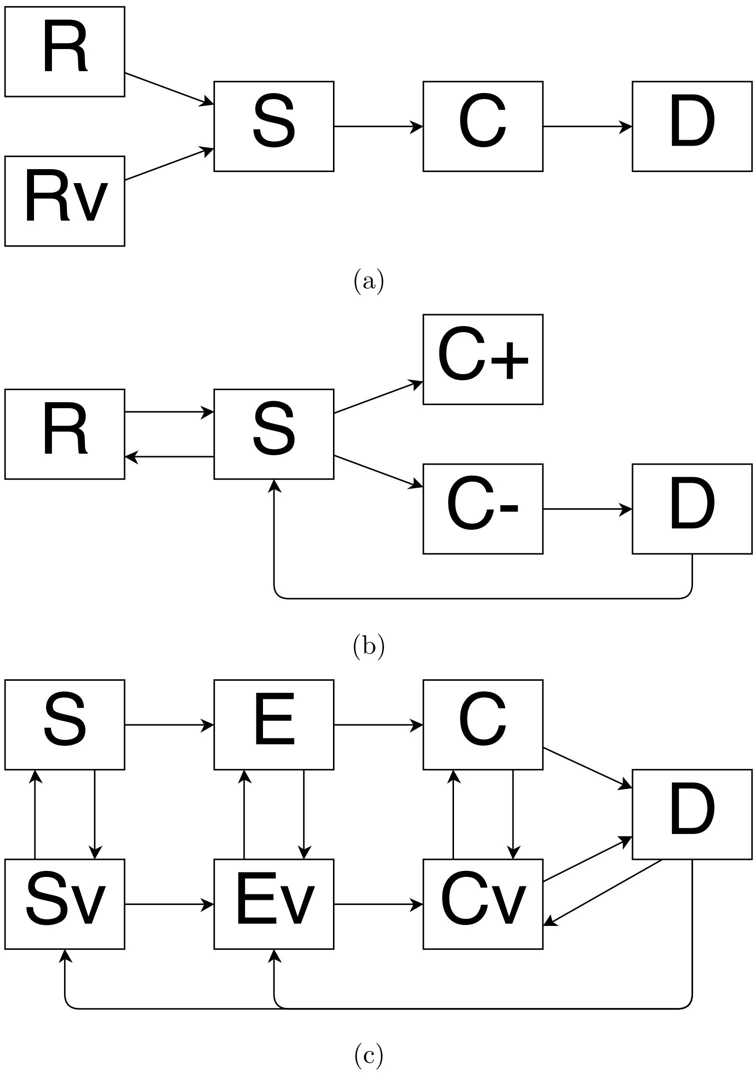

Figure 1: Three flow diagrams representing the gross structure of the models put forth by (a) Starr et al., (b) Lanzas et al. and (c) Yakob et al. Arrows represent permitted state changes. In each diagram where applicable: **R**: **R**esistant to colonisation; **S**: **S**usceptible to colonisation; **E**: **E**xposed; **C**: Asymptomatically **C**olonised; **D**: **D**iseased (symptomatically colonised). A state symbol followed by 'v' indicates vulnerability due to recent use of antibiotics. In addition + and **-** in (b) indicate ability and inability respectively to mount an effective immune response. In all models in addition to the transitions shown patients can be admitted or discharged in any state.

Postal Address: 111 Barry Street
c/- The University of Melbourne
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Email: enquiries@amsi.org.au
Phone: +61 3 8344 1777
Fax: +61 3 9349 4106
Web: www.amsi.org.au

the hospitals being modelled. The model developed by Yakob et al., does consider the effect of general antibiotic administration for the purpose of monitoring gut flora health, but assumes that unless a patient is in the diseased state that the antibiotics they are given have no chance of removing *C. difficile* . In addition the model by Jacob et al. does not consider infection from environmental sources.

The model developed by Starr et al. has two different states in which patients are immune: R and R_v. The the only way to enter these states is through admission into the hospital, which happens at two different, constant rates. The only way to leave them is to enter the one susceptible state, which occurs after a random time with exponential probability distribution. The time constant for each transition was determined using MCMC and the two found to be nearly equal (0.012 and 0.013) with highly overlapping 95% credible intervals ([0.008096, 0.01670] and [0.007781, 0.01988]). The numbers of patients in either state have no further effects on the dynamics of the model. Furthermore, the distinction between R and R_v was not used as a metric for success or failure of a course of treatment. Thus appears to be no reason to consider R and R_v separately.

The model

Of the three models considered here the most promising model which best represents current research is the 2013 model by Yakob et al. Their model has its own shortcomings so we propose a new model based on theirs. In form there are only two changes, both simple.

The first change is only minor a correction to the model so that in deterministic form, admissions balance hospital discharge and deaths. The rate of discharge from the hospital for each of the non-diseased states is given by κX where X is the state variable. Patients in the D state cannot be discharged but may die, governed by the rate constant μ. Thus if N is the sum of the state variables then the total discharge rate from the hospital is $m = \kappa(N - D) + \mu D$. To balance admissions with discharge we choose 7 parameters ϵ_X where X each state variable, such that each parameter is the proportion at admission in each state and as such sum to 1. Then the rate of admission into state X is simply $\epsilon_X m$.

The second change relates to the treatment of non-symptomatic patients with antibiotics. In most cases the recommended treatment for CDI is a course of specialised antibiotics which are effective against *C. difficile* . There are many such antibiotics, and some of these are prescribed commonly for conditions other than CDI (Debast et al. 2013). It thus makes sense to include a transition where an asymptomatically

Postal Address: 111 Barry Street
c/- The University of Melbourne
Victoria 3010 Australia
Email: enquiries@amsi.org.au
Phone: +61 3 8344 1777
Fax: +61 3 9349 4106
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colonised or exposed patient, being treated with antibiotics for a condition other than CDI is by coincidence cleared of *C. difficile* . Additionally, we may wish to determine the efficacy of preventatively administering antimicrobials effective against *C. difficile* in conjunction with any antibiotics administered which present an increased risk of CDI. For this reason we modify the modelled effect of administering antibiotics. In our model the prescription of antibiotics to an asymptomatic patient has probability τ of being as effective at clearing *C. difficile* from the gut as a course of targeted treatment given to symptomatically diseased patients. All possible transitions regarding antibiotic treatment are summarised in Table 2. A graphical overview of the whole model is given in Figure 2.

In addition to these structural changes we also make some adjustments to the parametrisation of the model. In particular, we allow q (called Q by Yakob et al.) to be any value between 0 and 1, allowing for the possibility that improved sanitation in response to the development of symptoms reduces but does not eliminate transmission. We also revise the estimates of ζ and μ, which are rates (with unit day^{-1}) but are estimated from clinical studies as if they were proportions by Yakob et al. We also simplify the ϵ coefficients, assuming that the proportion of patients at admission who have damaged gut flora is independent of the level of *C. difficile* colonisation. To this end we introduce 5 new parameters p_v, p_S, p_E, p_C, p_D such that

$$p_S + p_E + p_C + p_D = 1.$$

We then define the constants ϵ_X in terms of these constants

$$\begin{aligned}
\epsilon_S &= (1 - p_v)p_S \\
\epsilon_{S_v} &= p_v p_S \\
\epsilon_E &= (1 - p_v)p_E \\
\epsilon_{E_v} &= p_v p_E \\
\epsilon_C &= (1 - p_v)p_C \\
\epsilon_{C_v} &= p_v p_C \\
\epsilon_D &= p_D
\end{aligned}$$

which preserves

$$\epsilon_S + \epsilon_{S_v} + \epsilon_E + \epsilon_{E_v} + \epsilon_C + \epsilon_{C_v} + \epsilon_D = 1.$$

No estimate of β or individual ϵ values are given in Yakob et al. It is hard to estimate τ and q without additional data, however an estimate is not needed to assess the effect of possible preventative measures involving *C. difficile* effective antibiotics.

Postal Address: 111 Barry Street
c/- The University of Melbourne
Victoria 3010 Australia
Email: enquiries@amsi.org.au
Phone: +61 3 8344 1777
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Similarly, reasonable estimates of model parameters are informative but not required for sensitivity analysis of the model. The estimated values and physical meaning of parameters are summarised in Table 1. The coupled system of ODEs which describe the deterministic form of the model are as follows:

$$\frac{dS}{dt} = \epsilon_S m + \lambda S_v - \beta S \frac{C + C_v + Dq}{N} - (\alpha + \kappa) S$$

$$\frac{dS_v}{dt} = \epsilon_{S_v} m + \alpha S - \beta S_v \frac{C + C_v + Dq}{N} + (1 - \sigma)(\rho D + \tau\alpha(E + E_v + C + C_v)) \\ - (\lambda + \kappa) S_v$$

$$\frac{dE}{dt} = \epsilon_E m + \lambda E_v + \beta S \frac{C + C_v + Dq}{N} - (\alpha + \eta + \kappa) E$$

$$\frac{dE_v}{dt} = \epsilon_{E_v} m + (1 - \tau)\alpha E + \beta S_v \frac{C + C_v + Dq}{N} + \sigma(\rho D + \tau\alpha(E + E_v + C + C_v)) \\ - (\lambda + \eta_v + \kappa + \tau\alpha) E_v$$

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

$$\frac{dC_v}{dt} = \epsilon_{C_v} m + (1 - \tau)\alpha C + \eta_v E_v + \zeta D - (\lambda + \theta_v + \kappa + \tau\alpha) C_v$$

$$\frac{dD}{dt} = \epsilon_D m + \theta C + \theta_v C_v - (\zeta + \rho + \mu) D$$

where $N = S + S_v + E + E_v + C + C_v + D$ and $m = \kappa(N - D) + \mu D$ is the total rate of patient discharge and death.

Results and Discussion

To assess the sensitivity of the model to the parameters we first sampled the parameter space using latin hypercube sampling (LHS). Each parameter was sampled from a symmetric triangular distribution with mean as reported in Table 1. The width of triangular distribution for each parameter was equal to the mean value of the parameter. For each sample of parameters the solution to the ODE model was numerically estimated for $0 \leq t \leq 100$. Using the initial conditions

$$X(0) = \epsilon_X,$$

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c/- The University of Melbourne
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Phone: +61 3 8344 1777
Fax: +61 3 9349 4106
Web: www.amsi.org.au

Parameter	Definition	Estimate
λ	Recovery of gut flora (rate/day^{-1})	0.011
α	Rate of antibiotic treatment damaging to gut flora (rate/day^{-1})	0.11
β	Exposure (rate/day^{-1})	0.2*
η (η_v)	Establishment of asymptomatic colonies (rate/day^{-1})	0.2 (0.2)
θ (θ_v)	Onset of symptoms from asymptomatic state (rate/day^{-1})	0.04 (0.2)
ρ	Treatment of CDI (rate/day^{-1})	0.1
σ	Treatment failure (proportion)	0.2
ζ	Resolution of symptoms (rate/day^{-1})	0.05 (Bartlett 1984)
μ	Death from CDI (symptomatic patients only) (rate/day^{-1})	0.003 (Turgeon et al. 2011)
κ	Hospital discharge (rate/day^{-1})	0.17
q	Effectiveness of quarantine for symptomatic patients (0 is perfect)	0.2*
τ	Effectiveness of random antibiotic treatment (proportion)	0.2*
p_v	Proportion of patients at admission who have damaged gut flora	0.25
p_S†	Proportion of patients at admission who are susceptible to *C. difficile*	0.915*
p_E	Proportion of patients at admission who are exposed to *C. difficile*	0.04
p_C	Proportion of patients at admission who are asymptomatically colonised by *C. difficile*	0.04
p_D	Proportion of patients at admission who are symptomatically colonised by *C. difficile*	0.005*

Table 1: List of model parameters with description of medical significance. Parameters are the same as those given explicitly or described by Yakob et al. in their 2013 model unless given citation or marked otherwise. Parameters marked with a * indicate that the value is not based on medical data but that the value listed is that used as default in further simulation and as a mean in sensitivity analysis. † As by definition $p_S = 1 - (p_E + p_C + p_D)$, p_S it is not considered to be an independent parameter. The value given is calculated from the estimates of p_E, p_C, p_D and so is marked * because p_D is not based on medical data. p_S was not considered in the sensitivity analysis of deterministic model.

Description of Transition	Probability	State changes
Treatment of symptomatically colonised individuals		
Treatment effective, does not remove all *C. difficile*	$\rho\sigma D\delta t$	$D-1, E_v+1$
Treatment effective, removes all *C. difficile*	$\rho(1-\sigma)D\delta t$	$D-1, S_v+1$
Treatment of asymptomatically colonised individuals with healthy gut flora		
Treatment ineffective against *C. difficile*	$\alpha(1-\tau)C\delta t$	$C-1, C_v+1$
Treatment effective, does not remove all *C. difficile* *	$\alpha\tau\sigma C\delta t$	$C-1, E_v+1$
Treatment effective, removes all *C. difficile* *	$\alpha\tau(1-\sigma)C\delta t$	$C-1, S_v+1$
Treatment of asymptomatically colonised individuals with damaged gut flora		
Treatment ineffective against *C. difficile*	$\alpha(1-\tau)C_v\delta t$	No change
Treatment effective, does not remove all *C. difficile* *	$\alpha\tau\sigma C_v\delta t$	C_v-1, E_v+1
Treatment effective, removes all *C. difficile* *	$\alpha\tau(1-\sigma)C_v\delta t$	C_v-1, S_v+1
Treatment of exposed individuals with healthy gut flora		
Treatment ineffective against *C. difficile*	$\alpha(1-\tau)E\delta t$	$E-1, E_v+1$
Treatment effective, does not remove all *C. difficile* *	$\alpha\tau\sigma E\delta t$	$E-1, E_v+1$
Treatment effective, removes all *C. difficile* *	$\alpha\tau(1-\sigma)E\delta t$	$E-1, S_v+1$
Treatment of exposed individuals with damaged gut flora		
Treatment ineffective against *C. difficile*	$\alpha(1-\tau)E_v\delta t$	No change
Treatment effective, does not remove all *C. difficile* *	$\alpha\tau\sigma E_v\delta t$	No change
Treatment effective, removes all *C. difficile* *	$\alpha\tau(1-\sigma)E_v\delta t$	E_v-1, S_v+1
Treatment of susceptible individuals with healthy gut flora		
Treatment damages gut flora	αS	$U-1, U_v+1$
Treatment of susceptible individuals with damaged gut flora		
Treatment damages gut flora	αS_v	No change

Table 2: Probabilities in time δt of all transitions in our model involving the use of antibiotics and treatment of CDI as functions of the state variables. A number of the entries correspond to actions which have no effect but are included for completeness. Transitions which were not considered in the Yakob model are marked *

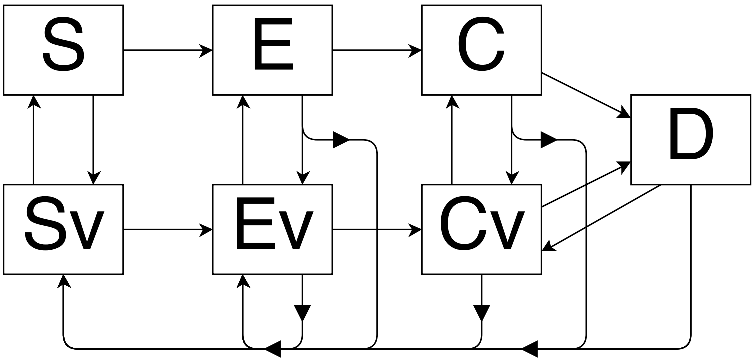

Figure 2: Flow diagrams representing the gross structure of our model. For legend see Figure 1.

where X is the state variable and ϵ_X is the mean (not the sampled) admission rate for state X. This was repeated for 2000 parameter samples. While numerically solving the system of ODEs four different monotonic increasing functions of t which measure hospital outcomes were calculated. These were (a) the total number of times a person becomes exposed to *C. difficile* in hospital, (b) the total number of times a person develops colonies of *C. difficile* in hospital, (c) the total number of times a person begins exhibiting symptoms in hospital and (d) the sum of these measures. Explicitly:

$$\begin{aligned}
f_a(t) &= \int_0^t \beta(S+S_v)\frac{C+C_v+Dq}{N}dt,\\
f_b(t) &= \int_0^t (\eta E + \eta_v E_v)dt,\\
f_c(t) &= \int_0^t (\theta C + \theta_v C_v)dt,\\
f_d(t) &= \int_0^t (\theta C + \theta_v C_v + \eta E + \eta_v E_v + \beta(S+S_v)\frac{C+C_v+Dq}{N})dt.
\end{aligned}$$

Then at each time step, t_n, and monotonic increasing function, $f_\alpha(t)$, the partial rank correlation coefficient (PRCC) for each parameter as a predictor for $f_\alpha(t_n)$ was calculated.

This whole process was performed for two cases. In the first case $\tau = 0$, where τ is the effectiveness against *C. difficile* of antibiotics prescribed generally in the hospital. In the second case, like the other parameters, τ was chosen from a symmetric triangular distribution with mean and width 0.2. The first case is for the most part identical to the Yakob model.

Postal Address: 111 Barry Street
c/- The University of Melbourne
Victoria 3010 Australia

Email: enquiries@amsi.org.au
Phone: +61 3 8344 1777
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Figure 3 and Figure 4 visualise these results, demonstrating that in both cases and for all measures of hospital health the model was most sensitive to β, κ, η, η_v, p_E and p_C. Of these, increasing κ improved (decreased) all the measures, while increasing the rest worsened (increased) all the measures. To improve the model it is of particular importance to improve our understanding of the range of these parameters in real hospitals.

The interaction between α, the rate of general prescription of antibiotics in the hospital, and τ, the effectiveness of these antibiotics against *C. difficile* , is of particular interest. The effect of non-zero τ can be observed by comparing Figures 3 and 4. In Figure 4, where $\tau = 0$, we observe that α had limited effect on (a) exposure of patients to *C. difficile* or (b) the formation of *C. difficile* colonies within patients, but greatly increased (c) symptomatic CDI incidence. In Figure 3 where τ has been sampled from a symmetric triangular distribution with mean and width 0.2, we see that increasing α significantly decreased (a) the exposure of patients to *C. difficile* and (b) the formation of *C. difficile* colonies within patients, but still increased (c) symptomatic CDI incidence. Increasing τ on the other hand decreased all three of these measures.

To further explore the effect of the widespread use of *C. difficile* effective antibiotics, the stochastic model (500 bed hospital for 1000 days) was run many times using a range of τ and α values but keeping all other parameters as given in Table 1. Figure 5 demonstrates the results from these simulations. With $\tau = 0$, increasing α increased the number of symptomatic CDI cases per 1000 bed days. With $0.15 < \tau < 0.3$, increasing α had little to no effect on the number of symptomatic CDI cases. For larger values of τ, increasing α reduced the number of symptomatic CDI cases.

For high (> 0.2) values of α, small increases in τ decreased symptomatic CDI incidence significantly (Figure 5c). In other words, in model hospitals with high antibiotic prescription rates modest improvements in the effectiveness against *C. difficile* of antibiotic treatments administered to all patients decreased the number of symptomatic CDI cases which occur per 1000 bed days.

For non-zero α increasing τ and for any τ increasing α decreased the effective mean number of infective individuals in hospital ($\overline{C + C_v + Dq}$) (Figure 5b), the number of colonisations which occurred in hospital (Figure 5c), and the net rate at which hospitals introduced or removed patients with some level of exposure to *C. difficile* to or from the community (Figure 5d).

Under both the sensitivity analysis of the deterministic model (Figure 3) and the parameter space exploration of the stochastic model (Figure 5), with $\tau = 0$ increasing α did not worsen any of the measures of hospital health other than symptomatic

CDI incidence and even caused modest improvements. A possible explanation for this unexpected observation is that increasing α moves more people to the vulnerable state, which — under the parameterisation in Table 1 — does not make patients any more susceptible to exposure and colonisation or increase infectivity, but does increase the rate at which colonised patients begin to exhibit symptoms. This means a larger proportion of the infective patients (C, C_v and D) are in the D state (Figure 5a). This decreases the effective number of infective individuals, $C + C_v + Dq$, as each D state patient is $q = 0.2$ times as infective (Figure 5b). As more patients are in the D class, the time spent colonised for the average patient is also reduced as D class patients are treated but C and C_v class patients are not. These two effects together then reduce the number of new infections occurring in hospital (Figure 5c & d).

Further Research

Figures 3 to 5 demonstrate the potential importance of the general use of *C. difficile* effective antibiotics in hospitals. However, before any clinical recommendations can be made the model must be refined by improving our understanding of the range of values which the parameters may take.

β cannot be estimated directly as it incorporates many factors such as hospital cleanliness, patient susceptibility, patient behaviour and minimum spore dose for viable infection. For this reason it can only be estimated by fitting the model to real hospital data using methods such as Markov Chain Monte Carlo (MCMC) estimation. As p_E is defined to be the proportion of patients admitted to the hospital with exposure to *C. difficile* but without observable colonies, it is not measurable and so must be estimated in much the same way as β.

κ is simple to estimate as it is the inverse of the average time a patient remains in hospital in a single visit. Similarly η, η_v, and p_C correspond to readily measurable quantities but unlike κ are specific to *C. difficile* , so will be further improved by an extensive survey of *C. difficile* literature and fitting to real hospital data.

Comparing the predictions made by the model to real hospital data will not only improve our estimates of the parameters in our model, but provide a way to validate the model structure. If the refined model does mimic real hospital data, the model may be used to make recommendations about the most effective means for reducing CDI incidence in hospitals and the exposure of the broader community to *C. difficile* caused by hospitals.

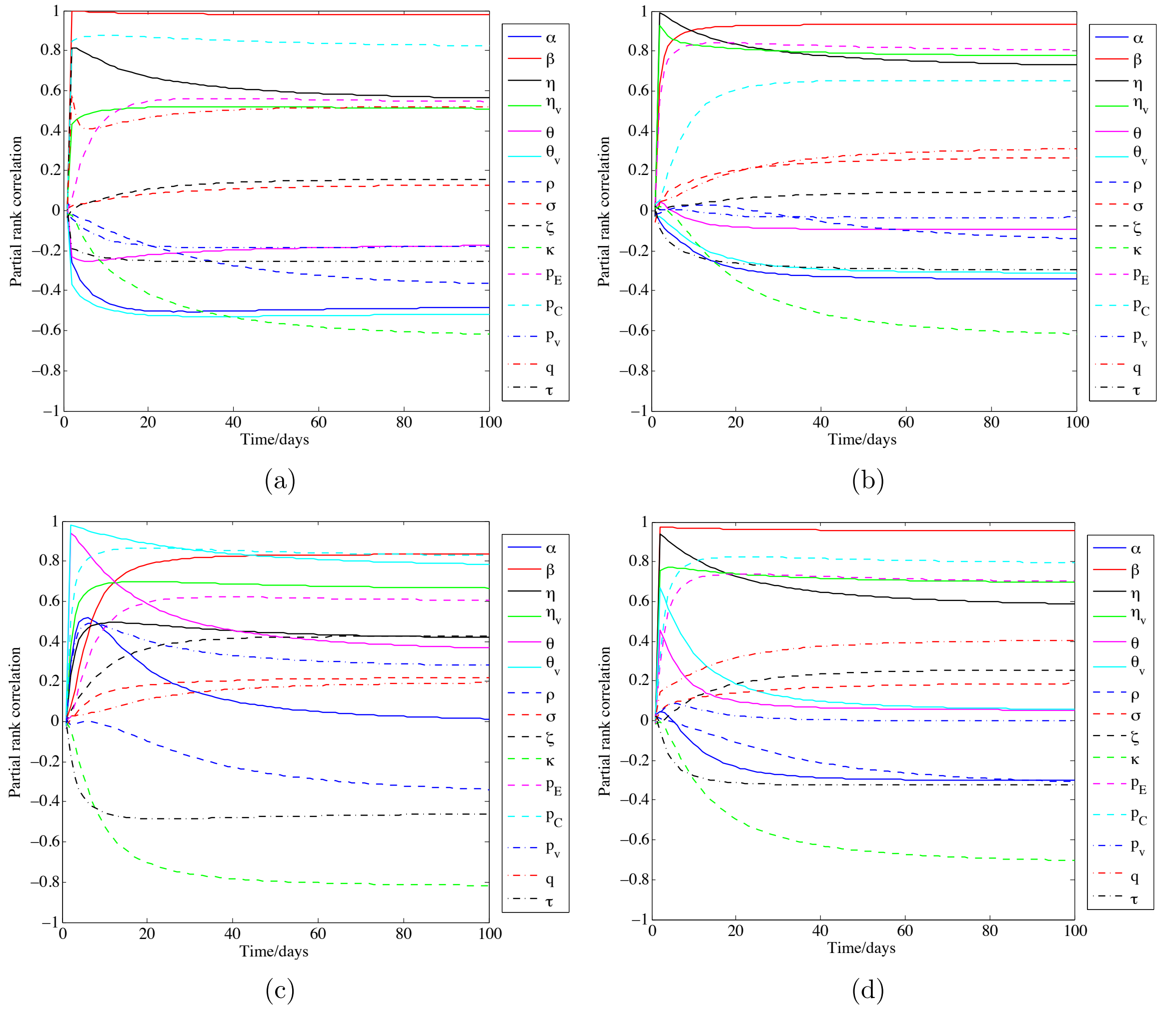

Figure 3: The sensitivity of our model to the parameters. The PRCC was calculated across 2000, 100 day runs of the ODE model where parameters were drawn using latin hypercube sampling from symmetrical triangular distributions ±50% around each parameter value listed in Table 1. Each subplot represents the sensitivity of a different measure. These measures are: (a) the total number of times a person becomes exposed to *C. difficile* in hospital, (b) the total number of times a person develops colonies of *C. difficile* in hospital, (c) the total number of times a person begins exhibiting symptoms in hospital and (d) the sum of these measures. All parameters were considered in our analysis but λ, μ and p_d have been omitted here, as the model was not sensitive to these parameters ($|PRCC| < 0.2$ for all measures and all time).

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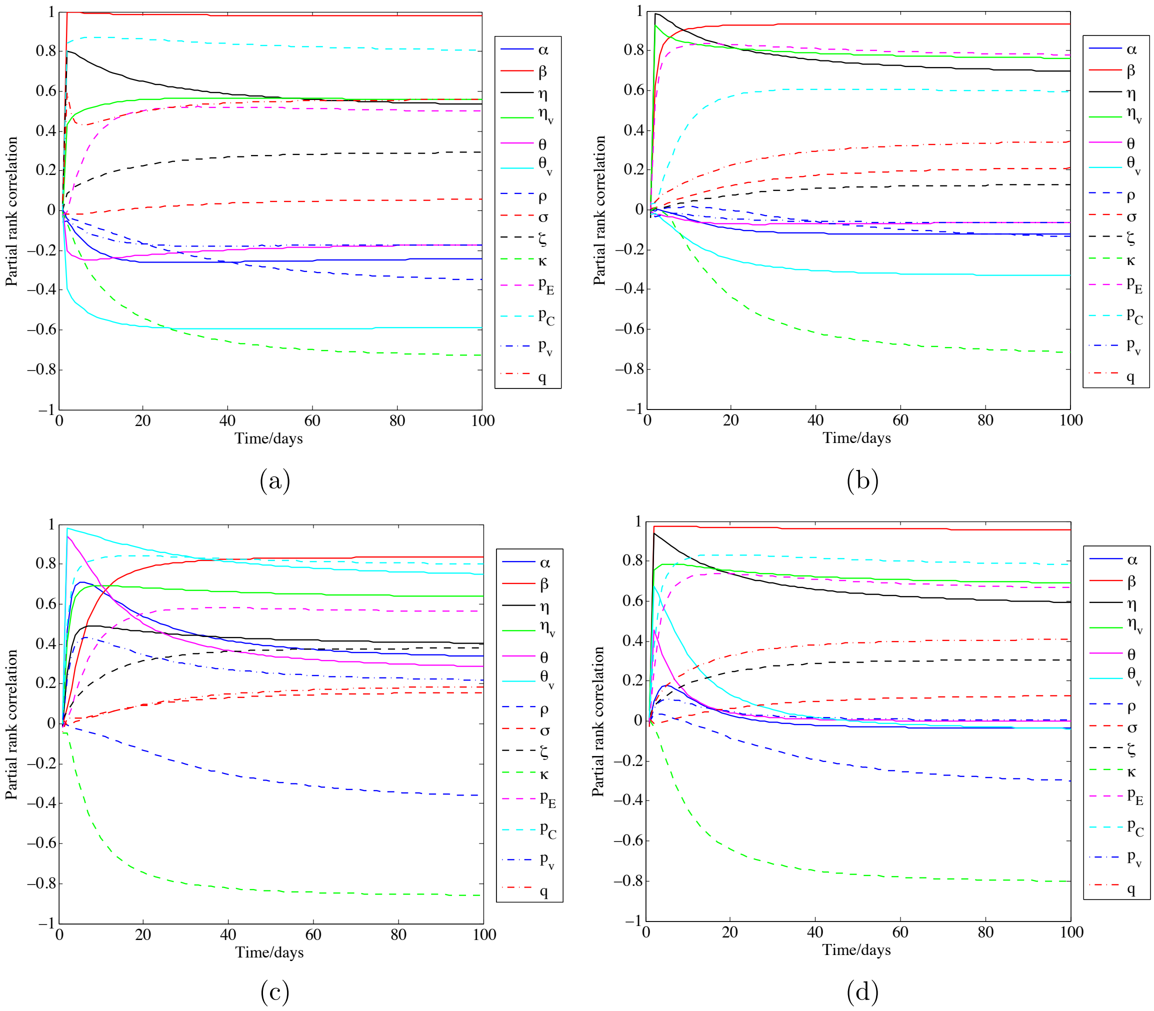

Figure 4: The sensitivity of our model to the parameters when $\tau = 0$. The PRCC was calculated across 2000, 100 day runs of the ODE model where parameters were drawn using latin hypercube sampling from symmetrical triangular distributions $\pm 50\%$ around each parameter value listed in Table 1. Each subplot represents the sensitivity of a different measure. These measures are: (a) the total number of times a person becomes exposed to *C. difficile* in hospital, (b) the total number of times a person develops colonies of *C. difficile* in hospital, (c) the total number of times a person begins exhibiting symptoms in hospital and (d) the sum of these measures. All parameters were considered in our analysis but λ, μ and p_d have been omitted here, as the model was not sensitive to these parameters ($|PRCC| < 0.2$ for all measures and all time).

Postal Address: 111 Barry Street
c/- The University of Melbourne
Victoria 3010 Australia
Email: enquiries@amsi.org.au
Phone: +61 3 8344 1777
Fax: +61 3 9349 4106
Web: www.amsi.org.au

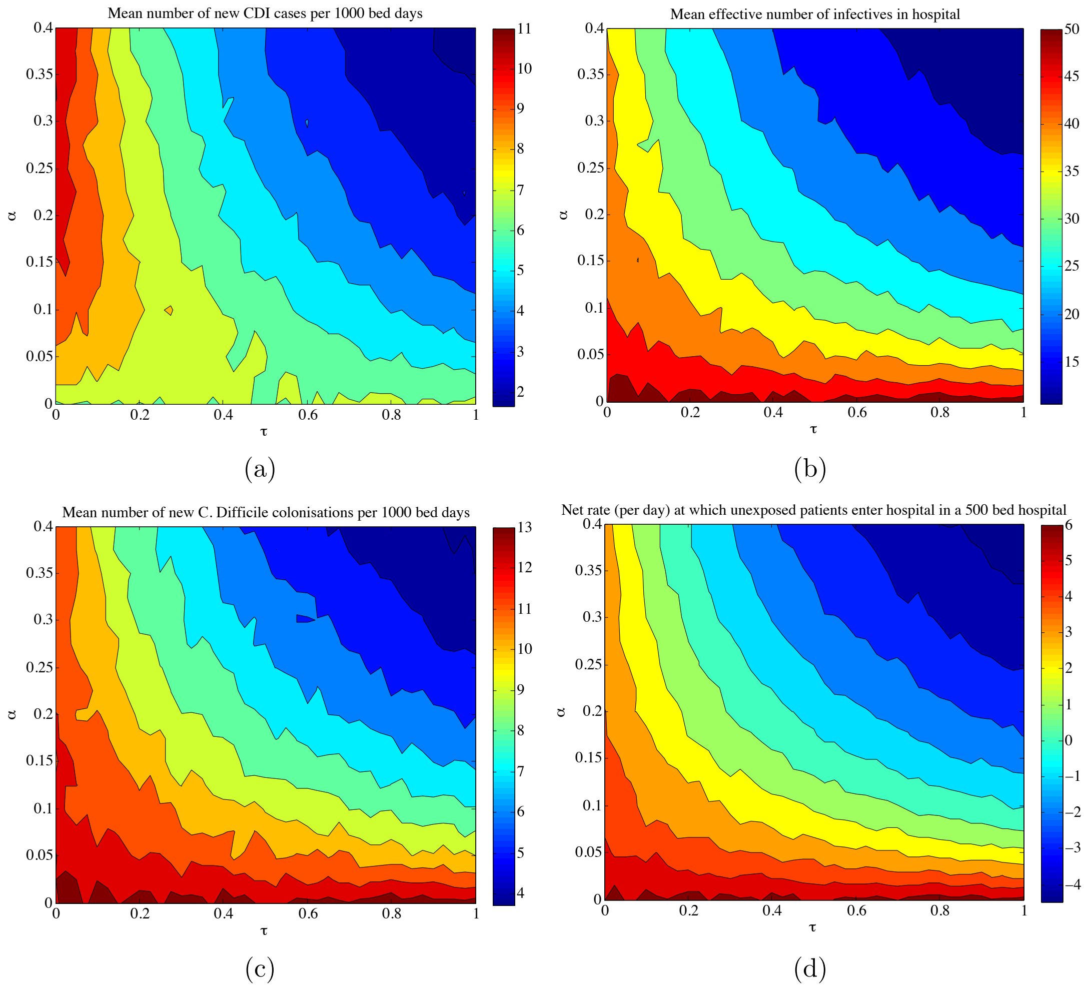

Figure 5: Indicators of hospital treatment and prevention efficacy as measured over 1000 day simulations of a 500 bed hospital with varying values of τ and α. All other parameters are as given in Table 1. (a) The mean effective number of infective individuals, $C + C_v + Dq$. (b) The mean number of C. difficile colonisation events per 1000 bed days. (c) The mean number of times a patient begins exhibiting symptoms per 1000 bed days. (d) The average number of patients who enter the hospital in S or S_v state per day less the number who leave in one of those states per day. As admissions balance discharges and deaths, this is also the average net number of people who are exposed to *C. difficile* by events within the hospital each day.

Postal Address: 111 Barry Street
c/- The University of Melbourne
Victoria 3010 Australia

Email: enquiries@amsi.org.au
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