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# A stochastic mathematical model of methicillin resistant *Staphylococcus aureus* transmission in an intensive care unit: Predicting the impact of interventions

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**Abstract**

*Objectives*: To estimate the transmission rate of MRSA in an intensive care unit (ICU) in an 800 bed Australian teaching hospital and predict the impact of infection control interventions.

*Methods*: A mathematical model was developed which consisted of four compartments: colonised and uncolonised patients and contaminated and uncontaminated health-care workers (HCWs). Patient movements, MRSA acquisition and daily prevalence data were collected from an ICU over 939 days. Hand hygiene compliance and the probability of MRSA transmission from patient to HCW per discordant contact were measured during the study. Attack rate and reproduction ratio were estimated using Bayesian methods. The impact of a number of interventions on attack rate was estimated using both stochastic and deterministic versions of the model.

*Results*: The mean number of secondary cases arising from the ICU admission of colonised patients, also called the ward reproduction ratio, $R_w$, was estimated to be 0.50 (95% CI 0.39–0.62). The attack rate was one MRSA transmission per 160 (95% CI 130–210) uncolonised-patient days. Results were not sensitive to uncertainty in measured model parameters (hand hygiene rate and transmission probability per contact).

Hand hygiene was predicted to be the most effective intervention. Decolonisation was predicted to be relatively ineffective. Increasing HCW numbers was predicted to increase MRSA transmission, in the absence of patient cohorting. The predictions of the stochastic model differed from those of the deterministic model, with lower levels of colonisation predicted by the stochastic model.

*Conclusions*: The number of secondary cases of MRSA colonisation within the ICU in this study was below unity. Transmission of MRSA was sustained through admission of colonised patients. Stochastic model simulations give more realistic predictions in hospital ward settings than deterministic models. Increasing staff does not necessarily lead to reduced transmission of nosocomial pathogens.


*Keywords:* Methicillin-resistant *Staphylococcus aureus* (MRSA); Bayesian; Modelling; Mathematical; Infection control

## 1. Introduction

Infections caused by antibiotic-resistant bacterial pathogens in the health-care setting are detrimental to patients and place a large burden on health-care institutions. *Staphylococcus aureus* is a common cause of hospital acquired blood stream infection and wound infection. Methicillin-resistant *S. aureus* (MRSA) leads to a higher mortality, morbidity (Engemann et al., 2003) and cost (Capitano et al., 2003) compared with methicillin-sensitive *S. aureus* (MSSA).

The proportion of isolates of *S. aureus* that are methicillin-resistant is increasing in many countries including Australia (Nimmo et al., 2003). It is likely that the increase in MRSA does not represent replacement of MSSA, but is an additional burden (Cooper and Lipsitch, 2004).

Methicillin resistance developed in *S. aureus* soon after this class of antibiotics was introduced (Ericksen and Erichsen, 1963). Most strains of health-care associated (HA) MRSA are also resistant to other classes of antibiotics

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including aminoglycosides and macrolides. Of even more concern is the recent observation that some MRSA isolates have been found to be resistant to glycopeptides (Bartley, 2002) and oxalidinones (Meka et al., 2004), the major alternative therapies for MRSA infection.

Antibiotic-resistant bacteria are believed to spread from patient to patient, principally via the hands of health-care workers (HCWs). Colonisation with MRSA frequently precedes infection. This transmissible, asymptomatic state will not be detected unless an active surveillance program is in place. Thus, halting the institutional spread of MRSA requires measures that affect colonised patients as well as those with overt infection.

Recommendations for the control of MRSA transmission include isolation (Garner, 1996) active surveillance cultures (Muto et al., 2003) and hand hygiene. While these guidelines are based on the best available evidence, few of the studies of hospital acquired infectious diseases use sound methodology (Cooper et al., 2003). The increase in the proportion of *S.aureus* isolates that are methicillin resistant in the face of infection control measures led to pessimism about their efficacy (Teare and Barrett, 1997). A recent study found that moving patients into single rooms or cohorted bays did not reduce MRSA acquisition (Cepeda et al., 2005), however this study screened for MRSA only weekly which may have led to long delays before colonised patients were removed from the general ward, diluting any benefit of isolation.

Mathematical models provide a means of predicting the likely impact of an intervention or the interaction of multiple interventions, capturing nonlinear transmission dynamics. Stochastic models have the additional advantage of predicting the expected variation in outcomes, which may be marked in small populations such as hospital wards. Statistical methods based on structured models provide a means of estimating transmission parameters from data.

In modelling community epidemics and emerging infectious diseases, the emphasis of model-informed infection control measures has been to achieve an effective reproduction ratio (the number of cases that occur due to the introduction of one infectious case, assuming a fully susceptible population) below unity. In the case of hospital associated pathogens such as MRSA, the mean number of secondary cases that arise within a ward during a single hospital admission (which we call the *ward reproduction ratio*, $R_w$) may be below unity, but colonised patients may go on to transmit MRSA in other wards and during subsequent hospital admissions leading to an overall reproduction ratio above unity (see Cooper et al., 2004 for full explanation).

In this study, we find a low *ward reproduction ratio*, $R_w = 0.5$. Frequent re-introductions of MRSA maintain the endemic prevalence. We therefore use attack rate, defined as the number of MRSA transmissions per uncolonised patient day, as our outcome measure when predicting the impact of interventions.

This study differentiates imported cases of MRSA from those that occur during ward stay. All new cases are assumed to arise from other colonised patients via the hands of HCWs (cross transmission). We utilised a mathematical model to quantify MRSA cross transmission in an Australian intensive care unit. We collected data on admission, discharge and colonisation events as well as other critical model parameters, hand hygiene compliance and transmission per contact, to estimate the MRSA attack rate and the *ward reproduction ratio*. We overcame the challenge of unobserved events by using a Bayesian framework and considering the MRSA acquisition date as a latent variable. Stochastic and deterministic realisations of the model gave predictions of the likely impact of interventions including changes in HCW/patient ratio, patient cohorting, hand hygiene, length of stay, admission prevalence, decolonisation and ward size on the attack rate.

This study extends previous models because all parameters used to estimate transmission were derived through ward observation directly or fitted to acquisition data. Ward observations running in parallel to the data collection gave us realistic values for hand hygiene compliance and probability of MRSA transmission from a colonised patient to HCW. For the simulation component of the study, we incorporate ward size as a parameter, not previously considered, and predict the impact of increases in staff levels if this leads to increased contact rates. The study later considers the effect of decolonisation based on parameters derived from an experimental study (de la Cal et al., 2004).

## 2. Model

Our ward transmission model was a modification of the susceptible–infectious (SI) model with migration, described by Bailey (1975). Versions of this model have been used previously to analyse nosocomial transmission data (Sebille and Valleron, 1997; Sebille et al., 1997; Cooper et al., 1999; Austin et al., 1999; Grundmann et al., 2002; Raboud et al., 2005).

### 2.1. Model description and assumptions

Fig. 1 illustrates the model for transmission of MRSA in an intensive care unit (ICU). It was assumed that transmission will occur with a probability, $p_{hp}$, when an MRSA contaminated HCW contacts an uncolonised patient and a probability, $p_{ph}$, when an MRSA colonised patient was contacted by an uncontaminated HCW. Given that patients carry MRSA for a long duration (the median MRSA patient carriage has been estimated to be 8.5 months (Scanvic et al., 2001) or 40 months (Sanford et al., 1994)) compared with their length of ICU stay (4 days observed in the current study) we made the simplifying assumption that the decolonisation rate, $d$, is zero in the absence of interventions. In contrast, HCWs were assumed

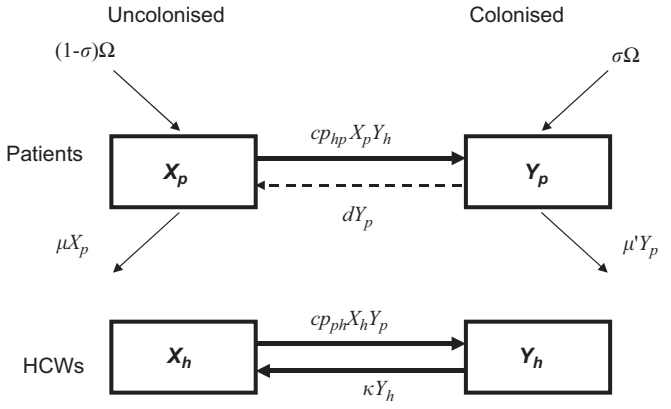


Fig. 1. Four compartment model of nosocomial pathogen transmission. Here $X_p$ is the number of uncolonised patients, $Y_p$ the number of colonised patients, $X_h$ the number of uncontaminated health-care workers, $Y_h$ the number of contaminated health-care workers. The parameters and their symbols are given in Table 1.

Table 1
Parameters used in the model for MRSA transmission

| Parameter | Symbol | Units |
|---|---|---|
| contact rate | $c$ | contacts $pt^{-1}\,HCW^{-1}\,day^{-1}$ |
| decolonisation rate | $d$ | $pt^{-1}\,day^{-1}$ |
| admission prevalence | $\sigma$ | – |
| admission rate (pt per day) | $\Omega$ | pt $day^{-1}$ |
| discharge rate of colonised pt | $\mu'$ | $day^{-1}$ |
| discharge rate of uncolonised pt | $\mu$ | $day^{-1}$ |
| transmission pt → HCW per contact | $p_{ph}$ | colonisation $contact^{-1}$ |
| transmission HCW → pt per contact | $p_{hp}$ | colonisation $HCW^{-1}$ |
| hand hygiene rate per HCW | $\kappa$ | $HCW^{-1}day^{-1}$ |

Key: pt patient, HCW health-care worker.

to be contaminated only until their next hand hygiene activity (which occurs at a rate, $\kappa$). Patients arrive at the ward at a rate, $\Omega$, and a proportion, $\sigma$ are colonised on arrival. Uncolonised and colonised patients are discharged at rates $\mu$ and $\mu'$, respectively. The contact rate $c$ is the number of contacts per patient per HCW.

The assumption of transient contamination of HCWs is justified by the established efficacy of hand hygiene activities for removing carriage (McBryde et al., 2004) and the fact that HCW carriage of MRSA is usually short term (Cookson et al., 1989). In this model we assumed that there was no direct patient to patient or HCW to HCW transmission. It was also assumed that there was no environmental reservoir contributing to transmission and that all patients who were colonised on admission were detected. While environmental sites have been shown to become contaminated by MRSA, it is uncertain whether this represents a significant source of MRSA transmission (Boyce et al., 1997). During the data collection phase, the HCW/patient ratio was assumed to be unity. This was in keeping with ward policy of providing at least one clinical nurse per patient. We also assumed homogenous mixing of patients and HCWs and time invariance of model parameters.

Fig. 1 illustrates the mathematical model of MRSA transmission. The parameters of the model are given in Table 1.

MRSA cases can arise from ward transmission (at a rate $cp_{hp}X_pY_h$) or from admission of newly colonised patients (at a rate $\sigma\Omega$). HCWs acquire MRSA via an interaction with a colonised patient at a rate proportional to the number of contacts with patients $cp_{ph}X_hY_p$; they are decontaminated at a rate dictated by hand hygiene, $\kappa Y_h$.

## 3. Data

### 3.1. Patients and setting

This study included all patients admitted to the ICU of a 800 bed tertiary referral teaching hospital (Princess Alexandra Hospital, Brisbane, Australia) from 8th August 2001 to 3rd March 2004 (939 days inclusive). The ICU bed capacity varied during the study from 16 to 22.

### 3.2. Surveillance of colonisation

During the investigation period, all patient admissions were recorded in the ApacheIII$^{TM}$ database. The mean number of inpatients who met inclusion criteria for the study each day was 15 (median 16).

Ward policy was to swab all patients on admission, on discharge from the unit and twice weekly for MRSA surveillance. Newly colonised patients were defined as those negative on admission who had a positive swab attributed to ICU stay (more than 48 h following ICU admission and less than 48 h following ICU discharge). An MRSA colonisation database was collected using pathology reports and record of prior colonisation on admission. For each of the 939 days of the study, the number of uncolonised patients on the ward, number of colonised patients on the ward and the number of new colonisations were recorded. Following discharge, each patient was categorised as not known to be colonised, known to be colonised prior to admission or newly colonised.

### 3.3. Parameter estimates

The admission prevalence of known MRSA colonised patients, $\sigma$ was 3% in this study. At the time of data collection, we estimated model parameters through ward observation. The hand hygiene compliance, $h$, was estimated to be 59% (395 hand hygiene episodes out of 668 hand hygiene opportunities observed in the study population (Whitby and McLaws, 2004)). This has a relationship with the hand hygiene rate as described in Section 4.1. The probability of MRSA transmission during a single contact between a colonised patient and an

uncolonised HCW was estimated to be 13% during the study period (17 positive hand cultures out of 129 patient visits found by McBryde et al., 2004). We used the data on all patient contacts (anyone who enters a patient bay) rather than strictly clinical contacts, which has a transmission probability of 17%, as measured by McBryde et al. (2004).

## 4. Methods

To quantify cross transmission of MRSA in our study population, we estimated the attack rate (number of transmissions per uncolonised patient day) and the ward reproduction ratio, $R_w$.

We have no direct estimate of contact rate, $c$, or probability of transmission from HCW to patient, $p_{hp}$. These two parameters are inseparable in the model, so we estimate the value of their product, the transmission parameter, $\phi = cp_{hp}$. The admission and discharge dates of patients are directly observed in this study and are thus incorporated deterministically. Colonisation status on admission is known (assumed to be perfectly observed).

In Section 4.1 we derive a form of the model equations that leaves only the transmission parameter, $\phi$, to be estimated. Section 4.2 explains how $\phi$ was inferred from the data. Section 4.3 describes how $\phi$ can be used to estimate $R_w$ and attack rate. Section 4.4 describes how the model structure can be used to predict the impact of interventions.

### 4.1. Formula for daily hazard of MRSA cross transmission

The daily hazard of MRSA cross transmission, $\lambda$, is given by

$$\lambda = \phi X_p Y_h. \tag{1}$$

We do not have direct observations of $Y_h$, however we derived a formula for $Y_h$ based on observable model parameters. Firstly, we assumed $\mathrm{d}Y_h/\mathrm{d}t = 0$. We base the assumption on the fact that decontamination of HCWs are known to be rapid (minutes to hours) compared with discharge or spontaneous decolonisation of patients (days to years, Boyce, 2005). The quasi-equilibrium value for the number of contaminated HCW, $Y_h$, which we denote by $\overline{Y}_h$ is given by

$$\overline{Y}_h = N_h \frac{cp_{ph} Y_p}{\kappa + cp_{ph} Y_p}, \tag{2}$$

where $N_h = X_h + Y_h$, is the number of HCWs.

During the study, we measured the pre-contact hand hygiene compliance, $h$. This was the proportion of patient contacts that were preceded by either hand washing or the use of a disinfectant hand spray or gel. A relationship between hand hygiene compliance and hand hygiene rate, $\kappa$, was derived by Cooper et al. (1999), namely,

$$h = \frac{\kappa}{\kappa + cN_p}, \tag{3}$$

where $N_p$ is the total number of patients.

Solving Eq. (3) for $\kappa$ and substituting this into Eq. (2) gives

$$\overline{Y}_h = N_h \frac{p_{ph} Y_p}{hN_p/(1-h) + p_{ph} Y_p}. \tag{4}$$

Noting that in this study $N_h = N_p = X_p + Y_p$, we have a revised expression for the rate of MRSA transmission to uncolonised patients, $\lambda$, given by

$$\lambda = \frac{\phi p_{ph} X_p Y_p (X_p + Y_p)}{(h(X_p + Y_p))/(1-h) + p_{ph} Y_p}. \tag{5}$$

The hand hygiene compliance, $h$, and the probability of MRSA transmission from patient to HCW, $p_{ph}$, were measured on the ward at the time of the study, leaving only one unknown value, the transmission parameter $\phi$, which was fitted to the data.

### 4.2. Bayesian inference to estimate $\phi$

Estimates of MRSA cross transmission were complicated by interval censoring of colonisation times. Colonisation events are asymptomatic so observations of MRSA acquisition consisted of the time of first detection, via routine swabs or clinical isolates. Assuming 100% swab sensitivity, transmission could have occurred at any point between the last negative swab or ICU admission (whichever was later) and the first positive swab or discharge from the ICU (whichever was sooner). We used a Bayesian framework to estimate the posterior probability density of the transmission parameter, $\phi$, given in the Appendix.

### 4.3. Estimates of the attack rate and the ward reproduction ratio

In this context, the *ward reproduction ratio*, $R_w$, is the expected number of MRSA cross transmissions resulting from a single colonised patient, assuming all other patients on the ward are susceptible. The model used in this study was a two population model in which there was no direct transmission between people of the same population type. The *ward reproduction ratio* is therefore the product of the expected number of transmissions from a single colonised patient to HCWs, $R_{ph}$, and the expected number of transmissions from a single contaminated HCW to patients, $R_{hp}$. Each component of $R_w$ can be calculated by multiplying the daily transmission probability by the expected duration of colonisation/contamination. Therefore,

$$R_w = \frac{c^2 p_{hp} p_{ph} (N_p - 1) N_h}{\mu' \kappa}. \tag{6}$$

By solving Eq. (3) for the hand hygiene rate, $\kappa$, and substituting it into Eq. (6) and using $\phi = cp_{hp}$ we get

$$R_w = \frac{\phi p_{ph}(1-h)(N_p-1)}{\mu' h}, \tag{7}$$

where $N_h$ and $N_p(=N_h)$ are the number of HCWs and patients in the ward, respectively. Therefore, the *ward reproduction ratio* will vary from day to day as the number of patients and HCWs changes, under the principle of pseudo-mass action. The estimated *ward reproduction ratio* was taken as the mean over the study period.

The hazard of patient transmission in the ward on day $t$ is $\phi Y_h(t)X_p(t)$. Therefore, the attack rate (the rate of transmission per uncolonised patient day) over the study period is given by

$$\mathrm{AR} = \phi \sum_{t=1}^{n} \overline{Y}_h(t). \tag{8}$$

### 4.4. Model for the impact of interventions

We used attack rate as the outcome measure to model the effect of a number of interventions: improving hand hygiene compliance, decolonisation, HCW/patient ratios with and without patient cohorting, ward size and patient discharge rate on the attack rate. We examined both deterministic and stochastic model predictions.

Estimated means of the parameters derived from the data were used as the default parameters. The ward size in the study was not fixed, however the ward ran at near maximum capacity much of the time, therefore new admissions were often limited by the rate of patient discharge. This justified the use of a simplifying assumption of fixed ward size to estimate the impact of interventions. We used the mean occupancy derived from the data to determine the number of patients in the ward, $n_p = 15$ (here we used a fixed value of occupancy as a parameter, $n_p$, rather than the variable, $N_p$). We also assumed that $N_h = \rho n_p$, where $\rho$ is the health-care/patient ratio. This simplifies the mathematical equations to

$$\begin{aligned}\frac{\mathrm{d}Y_p}{\mathrm{d}t} &= cp_{hp}(n_p - Y_p)Y_h - (d+\mu'(1-\sigma))Y_p \\ &\quad + \mu\sigma(n_p - Y_p),\end{aligned}$$

$$\frac{\mathrm{d}Y_h}{\mathrm{d}t} = cp_{ph}(\rho n_p - Y_h)Y_p - \kappa Y_h. \tag{9}$$

Note that we have now allowed decolonisation of patients, $d$, to be non-zero. The equilibrium attack rate is given by

$$\overline{AR} = cp_{hp}\overline{Y}_{h_e}, \tag{10}$$

where $\overline{Y}_{h_e}$ is the equilibrium value for $\overline{Y_h}$, obtained when $\mathrm{d}Y_p/\mathrm{d}t = \mathrm{d}Y_h/\mathrm{d}t = 0$.

In the stochastic version of the model, the probability during a small time interval, $\delta$, of transiting from one state to another is described by the equations

$$\begin{aligned}&\Pr(Y_p(t+\delta) = i+1 \,|\, Y_p(t) = i) \\ &\quad = cp_{hp}(n_p - i)\overline{Y}_h\delta + \mu\sigma(n_p - i)\delta + o(\delta),\end{aligned}$$

$$\begin{aligned}&\Pr(Y_p(t+\delta) = i-1 \,|\, Y_p(t) = i) \\ &\quad = (d+\mu'(1-\sigma))i\delta + o(\delta),\end{aligned}$$

$$\begin{aligned}&\Pr(Y_p(t+\delta) = i \,|\, Y_p(t) = i) \\ &\quad = 1 - cp_{hp}(n_p - i)\overline{Y}_h\delta - \mu\sigma(n_p - i)\delta \\ &\qquad - (d+\mu'(1-\sigma))i\delta + o(\delta),\end{aligned} \tag{11}$$

where $o(\delta)$ is the Landau symbol, denoting lower order terms of $\delta$. It was assumed that $\mathrm{d}Y_h/\mathrm{d}t = 0$. All other probabilities are $o(\delta)$.

The default value for the HCW/patient ratio, $\rho$, was unity. The default value for the decolonisation rate, $d$, was zero. Other default values were admission prevalence, $\sigma = 0.03$, discharge rate of colonised patients, $\mu' = 1/10.6$, corresponding to a mean length of stay of 10.6 days, discharge rate of uncolonised patients, $\mu = \frac{1}{4}$, corresponding to a mean length of stay of 4 days, probability of transmission from colonised patient to HCW per contact, $p_{ph} = 0.13$, hand hygiene compliance, $h = 0.59$. In the simulations, for each set of parameters, the ward was assumed to start with no colonised patients, the burn-in period was 1000 days and the predicted attack rate was derived from the next 939 simulated days. Stochastic results were based on 1000 simulations for each set of parameters, and the 2.5–97.5 percentile ranges were determined.

By leaving all other parameters at their default values and modifying $h$, $\mu'$, $\mu$ and $\sigma$, we simulated the effects of changes in hand hygiene compliance, discharge rate of colonised and uncolonised patients and admission prevalence, respectively. By changing $d$ from zero to 0.05, we simulated the effect of decolonisation. The latter decolonisation rate was chosen based on a study by de la Cal et al. (2004) in which patients were given enteral vancomycin in an attempt to eradicate MRSA.

Cohorting was simulated by reducing the number of "effective contacts". We assumed that cohorting was non-selective. That is, that HCWs cared for a cohort of patients who could be a mix of colonised and uncolonised patients. The smaller the group in the cohort, the more likely that a given contact is a return contact and thus not an "effective contact". When maximum cohorting is taking place, we assume that a proportion of contacts equal to the HCW/patient ratio, $\rho$, pose no risk (when $\rho \geqslant 1$ all cohorted contacts pose no risk).

Our model defined $c$ as the number of contacts per patient per HCW. By examining the effect of increasing staff patient ratio, $\rho$, we assume that each HCW has a fixed number of contacts and increasing staff increases contacts. To extend this simulation to allow for changes in patient numbers but continuing to assume a fixed number of contacts per HCW, one could modify the contact rate,

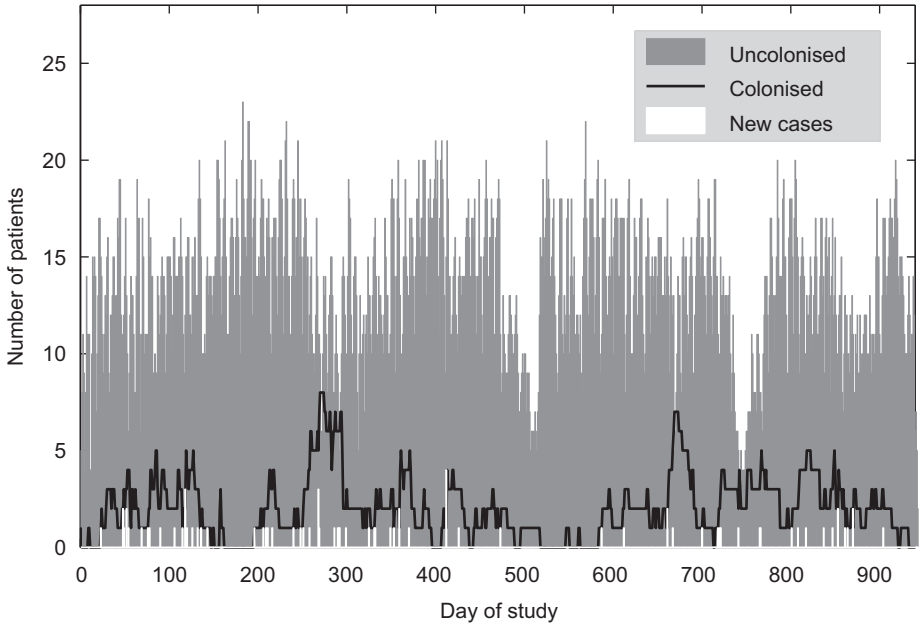


Fig. 2. Data collected over period of study. The grey bar plot indicates the number of uncolonised patients on each day, the black line plot indicates the number of colonised patients and the white bar plot the new acquisitions.

$c^* = c(n_p/N_p)$, where $n_p$ is the default number of patients and $N_p$ is the actual number of patients. We could alternatively simulate a situation where patients have a fixed number of contacts and increasing staff does not increase contacts. Such a simulation would require modifying the contact rate to $c^*$, where $c^* = c/\rho$.

## 5. Results

During the study period, 3329 patients met inclusion criteria. Of these, 100 patients were known to be colonised on admission and 77 met the criteria for new colonisation. Fig. 2 summarises the data.

### 5.1. Estimate ward transmission: attack rate and the ward reproduction ratio

The posterior probability distribution of the *ward reproduction ratio*, $R_w$, is shown in Fig. 3(a). The estimated mean value of the reproduction ratio was 0.50 (95% CI 0.39–0.62 ). The posterior probability distribution of the attack rate is shown in Fig. 3(b). The estimated mean was 0.0062 transmissions per uncolonised patient day (95% CI 0.0048–0.0076), or approximately one new acquisition per 160 uncolonised patient days.

### 5.2. Predicted impact of interventions

Fig. 4 shows the predicted impact of ward interventions. The model predicts that the attack rate would increase dramatically should the hand hygiene compliance fall below 40%. A hand hygiene compliance of 48% would increase the *ward reproduction ratio* to unity. Fig. 4(b) shows the effect of changing the discharge rate of colonised patients, $\mu'$, leading to a reciprocal change in expected duration of stay. The response curve was sigmoidal in shape. Increasing the mean time on ward following colonisation to 21 days would lead to the *ward reproduction ratio* exceeding unity.

The predicted effect of increasing length of stay of all patients (Fig. 4(c)) is an increase in attack rate but this increase is much less than the effect of increasing length of stay of colonised patients alone. The response of attack rate to doubling the admission prevalence from the current 3% to 6% is a predicted increase in attack rate from one transmission per 160 uncolonised patient days to one per 105 uncolonised patient days (Fig. 4(d)).

We compared a strategy of MRSA decolonisation at a rate of 0.05 per day with no decolonisation. The reduction in attack rate was modest, from 0.0061 to 0.0034, with overlapping 95% ranges for the stochastic simulations.

We investigated the predicted impact of changing the HCW/patient ratio. In the upper curve of Fig. 5, there is no patient cohorting and increasing HCW numbers increases cross transmission. In the other curves, we assumed that HCWs can be assigned to a fixed group of patients. Successively lower curves in Fig. 5 represent greater proportion of HCWs involved in cohorting. The lower curve in Fig. 5 gives the predicted change in attack rate as HCW/patient ratios change when 100% of HCWs practise cohorting. Once the HCW/patient ratio reached 1:1 there was no MRSA transmission.

Fig. 6 shows the effect of reducing ward size on attack rate, assuming the number of contacts per HCW is constant. The deterministic curve is compared with the interquartile range in the boxplots of 1000 stochastic simulation results. The attack rate in the deterministic model, unsurprisingly, does not change with ward size. The

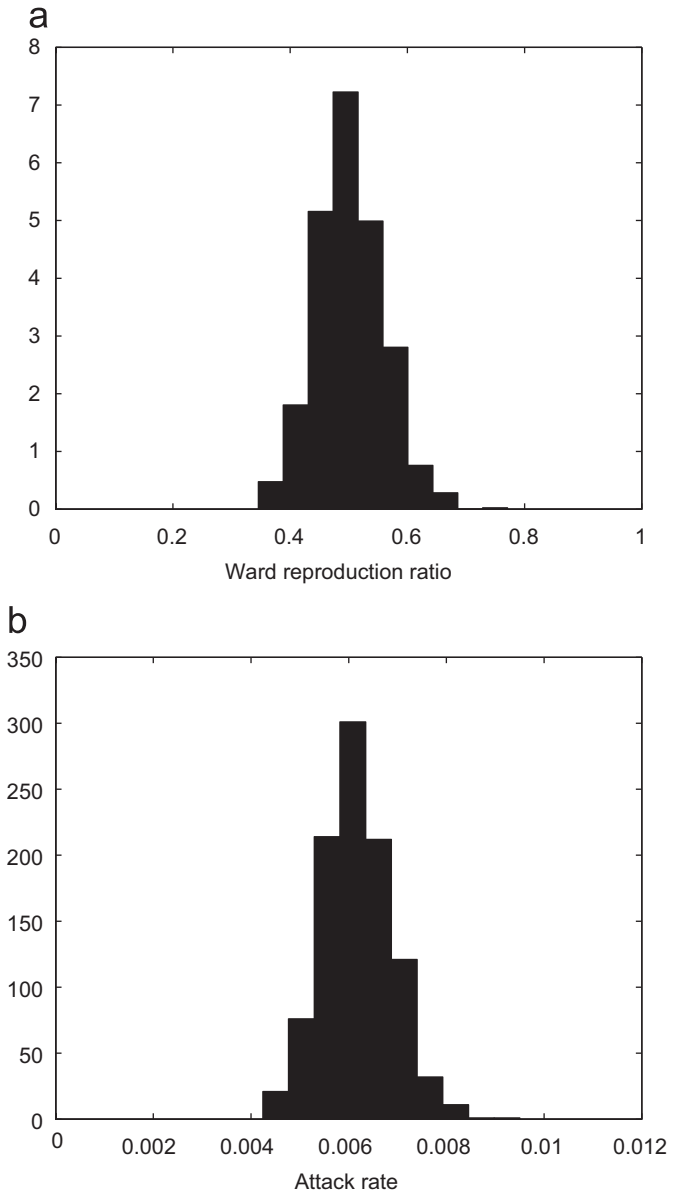


Fig. 3. (a) posterior probability density of ward reproduction ratio; (b) posterior probability density for the attack rate per uncolonised patient day.

stochastic model shows reduced median attack rate, particularly when the ward size reduces below 10 patients. This represents an increased proportion of time spent in stochastic fade-out in small wards.

In several plots, the attack rate predicted by the deterministic model was higher than that predicted by the stochastic model. Often, the deterministic predictions were outside the stochastic 95% variability range of the corresponding stochastic model.

### 5.3. Model adequacy

A parametric bootstrap analysis was used to determine model adequacy. This process involves simulating data from the model, using ward observations (number of uncolonised patients and admission of known colonised patients) and the estimated transmission parameter, $\phi$. The methodology described in this paper was then applied to the simulated data to estimate the mean of the marginal posterior distribution of the transmission parameter, the *ward reproduction ratio* and the attack rate. The study found that this gave an unbiased estimate of the transmission parameter.

## 6. Discussion

We used a Bayesian framework to quantify MRSA transmission and estimate the *ward reproduction ratio* of MRSA in an ICU in a large teaching hospital. The Bayesian methodology allowed us to incorporate unseen events, namely, the time of MRSA transmission.

This study used a four compartment modified SI model with migration. Ward observations of hand hygiene compliance and transmission probability per contact gave us estimates of all but one model parameter, which was readily fitted to the data.

We found that, in the ICU under investigation, the *ward reproduction ratio* was below unity (0.50, 95% CI 0.39–0.62). This compares with the finding by Grundmann et al. (2002), also studying MRSA in an ICU, of a *ward reproduction ratio* of 1.52, when interventions were included. The hand hygiene compliance in the study by Grundmann et al., 2002 was similar to the current study, however the length of stay of colonised patients was considerably longer, possibly accounting for some of the difference. A study by Austin et al. (1999) on vancomycin-resistant enterococci transmission found a *ward reproduction ratio* of 0.7 when infection control interventions were in place. The study by Austin et al. (1999) found a hand hygiene compliance of 50% and length of stay of colonised patients of around 15 days, both of which would be expected to lead to higher reproduction ratios than that found in the current study.

The current study found that the predicted transmission rate did not dramatically change as the *ward reproduction ratio* went above unity in simulations involving changing the hand hygiene compliance and duration of stay. This finding differs from studies of community epidemics in which the basic reproduction ratio represents a threshold value, below which only very limited transmission occurs. When there is continued migration of colonised patients, as occurs in most hospitals with MRSA, the reproduction ratio does not discriminate between high levels and low levels of transmission; nor does it quantify risk of colonisation to individual patients. We therefore recommend that the attack rate be used as a measure of efficacy of interventions in this setting.

Our model predicted that improving hand hygiene compliance would be the most effective method of preventing MRSA transmission. Small increments in compliance resulted in large nonlinear reductions in attack

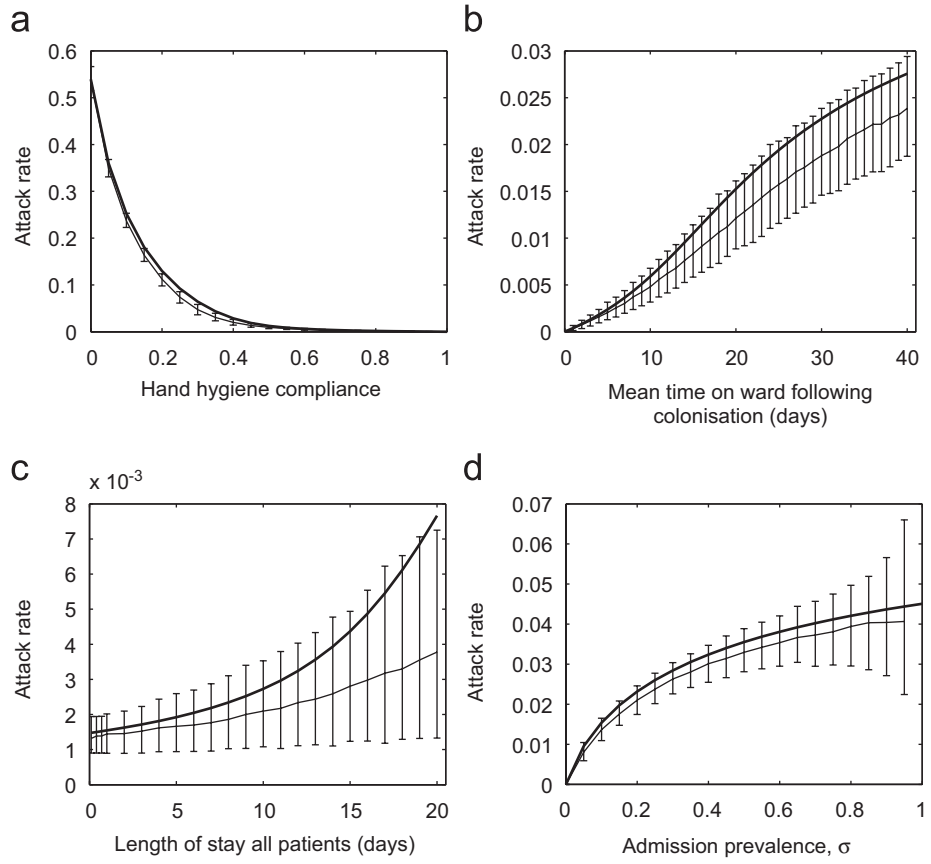


Fig. 4. Effect of changing parameters on attack rate. The bold line represents the prediction of the deterministic model, the feint line represents the mean of the stochastic model predictions with error bars giving the 2.5–97.5% interval. (a) Effect of hand hygiene compliance on attack rate. (b) Effect of length of stay of colonised patients on attack rate. (c) Effect of length of stay of all patients on attack rate. (d) Effect of admission prevalence on attack rate.

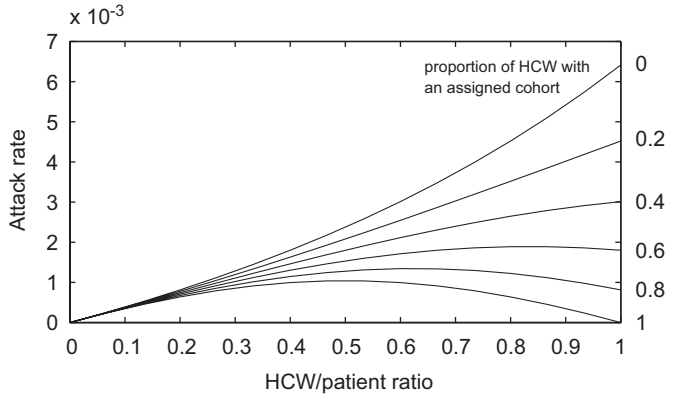


Fig. 5. Effect of cohorting on attack rate. The impact of HCW patient ratio varies depending on the proportion of contacts that are able to be cohorted. The deterministic results only are given here.

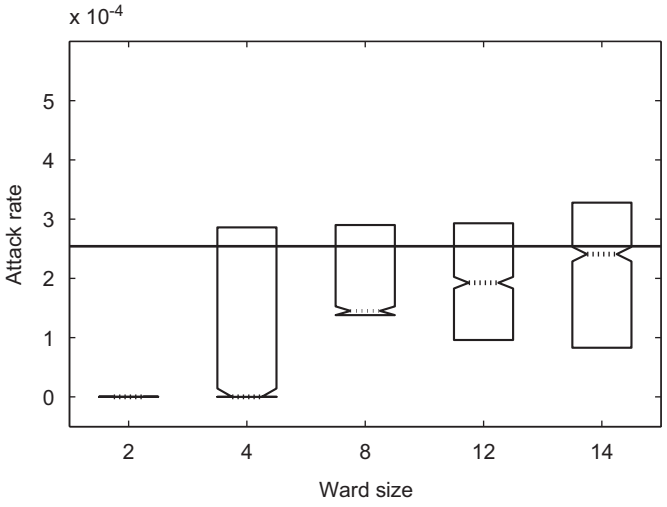


Fig. 6. Effect of ward size on attack rate. The deterministic value (horizontal line) is compared with the median (broken line) and interquartile range (boxplots) of 1000 stochastic simulation results.

rate. If the compliance were to fall below 40%, there would be a dramatic rise in attack rate, as predicted by our model. Such a rate is commonly encountered in hand hygiene studies, prior to interventions (Johnson et al., 2005; Amazian et al., 2006; Wong and Tam, 2005).

The model predicted that patient decolonisation would not be as effective as hand hygiene. This is because the time frame to decolonisation (mean of 20 days) was long relative to the mean length of stay. The time to decolonisation was estimated from a paper by de la Cal et al. (2004). From this paper, we estimated the decolonisation rate to be 0.05 per colonised patient. It could be argued that while

decolonisation is slow, the transmissibility may be reduced even in patients who remain colonised. If so the impact on transmission of decolonisation would be greater than predicted by this model.

A finding in this study which differs from previous studies (for example D'Agata et al., 2005) was that increasing HCW levels may lead to an increase in attack rate. An analysis of intensive care workload studies found that, in the presence of a staff deficit, some studies report that the productivity of staff reaches a limit, leading to inability to complete tasks involving patient care (Carayon and Gürses, 2005). In this circumstance, the number of contacts per day is determined by the number of available staff rather than the number of patients, and the number of contacts will increase as staff level increases. We aimed to capture this circumstance in our model. When the contacts were not cohorted, increased HCW/patient ratios resulted in a dramatic rise in attack rate, as predicted by the model. When cohorting was introduced, the model predicted an initial rise in attack rate as HCW numbers increase, followed by a decline as the increased HCW ratio permitted greater cohorting. Other factors such as improved compliance with hand hygiene could mitigate against increase in attack rate and could explain the increased transmission associated with staff deficit in the study by Grundmann et al. (2002).

When considering patient cohorting, one needs to keep in mind that cohorting measures are usually only able to be carried out by nurses. We found in our hospital that doctors, who are not involved in cohorting, have a lower than average hand hygiene compliance rate (McBryde et al., 2004). The impact of this on transmission could be predicted by relaxing the assumption of uniformity of behaviour within the HCW group.

The stochastic version of our model gave different results from the deterministic version. This is accounted for by frequent "fade outs" in MRSA colonisation leading to episodes in which transmission cannot take place in the stochastic model. These findings are not unexpected in models of small populations but reinforce the need to incorporate stochasticity in simulations of interventions.

We found that the *ward reproduction ratio* was below unity in the ICU in our study. Therefore, in order for MRSA to persist it needs to be imported. This leads us to question why MRSA continues to be problematic in the health-care facility in the study. The answer probably lies in the fact that patients continue to transmit MRSA after leaving ICU. Colonised patients may transmit MRSA in other hospital wards, in nursing homes, in the community and on readmission to hospital (Cooper et al., 2004). Although the *ward reproduction ratio* within the ICU was less than unity, the overall reproduction ratio of MRSA colonisation could be greater than unity. The estimate for the *ward reproduction ratio* was not sensitive to the measurement uncertainties in the model parameters.

In future studies, other possible modes of transmission need to be considered, including an environmental reservoir, transmission from HCWs with chronic MRSA carriage, or unobserved colonisation events, including patients harbouring MRSA on admission without being detected. Economic modelling of the cost and utility of different interventions would be a useful adjunct to future studies in this area.

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## Appendix A. Bayesian estimation of the transmission parameter

Transmission events were treated as latent variables in the model. The full conditional probability of the transmission parameter, $\phi$, given a complete data set, $\boldsymbol{D}$, including daily numbers of uncolonised, colonised patients and transmission events (latent variables) is given by

$$p(\phi\,|\boldsymbol{D}) \propto \pi(\phi)L(\boldsymbol{D}|\phi), \tag{A.1}$$

where $\pi(\phi)$ is the prior probability of $\phi$ and $L(\boldsymbol{D}|\phi)$ is the probability of the complete data set.

The marginal posterior probability density of the transmission parameter, $\phi$, can be obtained by summation of over all possible values of the latent variables

$$p(\phi\,|\boldsymbol{O}) \propto \pi(\phi)\sum_{A} L(\boldsymbol{D}|\phi), \tag{A.2}$$

where $\boldsymbol{O}$ is the observed data and $\boldsymbol{A}$ is the vector of latent variables ($\boldsymbol{D} = \{\boldsymbol{O}, \boldsymbol{A}\}$). Here, we take $\boldsymbol{A}$ to be the exact day of MRSA acquisition and the resulting numbers of colonised and uncolonised patients on each day.

A Markov chain Monte-Carlo (MCMC) approach was used to estimate the posterior probability density of the transmission parameter, $\phi$. A prior probability, $\pi(\phi)$, was assigned to $\phi$, the likelihood of the data, $L(\boldsymbol{D}|\phi)$, was calculated. Latent variables and the transmission parameter were updated using a Gibbs steps and the process was iterated.

Each of the component of the MCMC is explained in turn.

### *A.1. Likelihood of the complete data set*

We used a piecewise constant hazard assumption (Aslanidou et al., 1998) to calculate the likelihood of the complete data set. The complete data set consisted of the daily number of MRSA colonised patients, uncolonised patients and the number of MRSA cross transmissions. We assumed that events on the same day were conditionally independent (given the known number of colonised

patients on the ward at the end of the previous day). We assumed that a newly colonised patient did not become colonised until the end of the time interval (one day), and therefore could not cause transmissions until the following day.

The complete data set $\boldsymbol{D}$ consists of three vectors, $[\boldsymbol{X}_p, \boldsymbol{Y}_p, \boldsymbol{Z}]$, where $\boldsymbol{X}_p$ is the vector of the number of uncolonised patients on each day of the study, $\boldsymbol{Y}_p$ is the vector of the number of colonised patients on each day of the study, and $\boldsymbol{Z}$ is the vector of the number of new acquisitions on each day of the study.

New acquisitions of MRSA were assumed to follow a Poisson process with a rate that was constant over each time increment of one day. This rate was the daily hazard of transmission, $\lambda(t)$, calculated using Eq. (5).

Let

$$a(t) = \frac{p_{ph} X_p(t) Y_p(t)(X_p(t) + Y_p(t))}{(h(X_p(t) + Y_p(t)))/(1-h) + p_{ph} Y_p(t)}, \tag{A.3}$$

so that $\lambda(t) = \phi a(t)$. The likelihood of the complete data over the duration of the study ($n = 939$ days) is determined using

$$L(\boldsymbol{D}|\phi) \propto \phi^{\sum_{t=1}^{n} Z(t)} \mathrm{e}^{-\phi \sum_{t=1}^{n} a(t)}. \tag{A.4}$$

Here, multiple events were allowed to occur during a given time increment and the likelihood was calculated at integer times (days) making no specific allowance for this being an approximation for continuous time. Becker (1989, Chapter 6.3) suggests that this approximation is sufficiently accurate for applications where the value of the rate parameter is relatively small.

### A.2. Gibbs update for the transmission parameter, $\phi$

The Gamma prior distribution is a conjugate prior to the likelihood calculation given in Eq. (A.4). The posterior probability of the transmission parameter, $\phi$, given the complete data set, and assuming a Gamma$(\alpha, \beta)$ prior for $\phi$, is given by

$$p(\phi|\boldsymbol{D}) \propto Gamma(\phi; \alpha, \beta) \phi^{z} \mathrm{e}^{-\phi \sum_{t=1}^{n} a(t)},$$

giving

$$\phi|\boldsymbol{D} \sim Gamma\left(\alpha + z, \beta + \sum_{t=1}^{n} a(t)\right), \tag{A.5}$$

where $z$ is the total number of cross transmissions over the duration of the study.

### A.3. Latent variable imputation

The vector of latent variables, $\boldsymbol{A}$, consists of the MRSA acquisitions times for the 77 newly colonised patients, as well as the number of colonised and uncolonised patients each day that are dependent on those acquisition times. For each iteration of the Markov chain, the vector was updated by drawing new values from the full conditional distribution.

For each newly colonised patient, the date of admission to the ICU or last negative swab (whichever was later) was taken to be the earliest possible day on which MRSA acquisitions could have occurred ($t_{\min}$) and the discharge date or date of first positive swab (whichever was sooner) was taken to be the latest possible day on which MRSA acquisitions could have occurred ($t_{\max}$). The likelihood of acquisitions occurring on each of these days was calculated. An inferred day of acquisition was drawn from the weighted likelihoods.

Let $T_i$ be the day on which patient $i$ acquires MRSA. Then $T_i$ can take the values $(t_{\min}, \ldots, t_{\max})$. Transmission can take place only once and, using discrete time intervals of one day, $T_i$ has $t_{\max} - t_{\min} + 1$ possible values. The full conditional posterior distribution for $T_{ik}$ is given by

$$p(T_i = k|X_{\mathbf{s},k}, Y_{\mathbf{s},k}, Z_{\mathbf{s},k}, \phi) \propto \prod_{t=1}^{n} [\lambda_{\mathbf{s},k}(t)]^{Z_{\mathbf{s},k}(t)} \mathrm{e}^{-\lambda_{\mathbf{s},k}(t)}, \tag{A.6}$$

where $X_{s,k}(t)$, $Y_{s,k}(t)$, $Z_{s,k}(t)$ and $\lambda_{s,k}(t)$ are the numbers of uncolonised, colonised, acquisitions and daily hazard function, respectively, on day $t$, given that acquisition for patient $i$ occurs on day $k$ and given the current state, $\mathbf{s}$, of values of $T_j, j \neq i$. Only part of the complete likelihood involves $T_i$, therefore the likelihood that patient $i$ acquired MRSA on day $k$, $L_{ik}$, is given by

$$L_{ik} \propto \prod_{t=t_{\min}}^{t_{\max}} \lambda_{s,k}(t)^{Z_{s,k}(t)} \mathrm{e}^{-\lambda_{s,k}(t)}. \tag{A.7}$$

The sampling distribution for $T_i$, $p(T_i = k)$, in the MCMC update for $T_i$, is proportional to the likelihood given by the right-hand side of Eq. (A.7).

### A.4. Incorporating uncertainty of model parameters

Because two of the parameters in the study (hand hygiene compliance, $h$, and the transmission from colonised patient to HCW, $p_{ph}$) were estimated by direct observation on the ward, there is uncertainty in these estimates. The transmission parameter, $\phi$, was estimated from the data. We need to incorporate the uncertainty of the measured parameters into the estimate for the transmission parameter, $\phi$.

The posterior probability density for hand hygiene compliance, $h$, was derived using a $Beta(1, 1)$ conjugate prior probability density (Gelman et al., 2004) and the data available from ward observations (the sufficient statistics were the total number of hand hygiene opportunities observed, $m$, and the number in which hand hygiene compliance occurred, $l$). We assumed that each hand hygiene opportunity was an independent Bernoulli trial. The posterior probability density for the hand hygiene compliance is given by

$$p(h|l, m) \propto \pi(h) p(l, m|h).$$

That is

$$h|l,m \sim Beta(1+l, 1+m-l). \quad (A.8)$$

The posterior probability density for the probability of transmission from a colonised patient to a HCW was derived using the same methodology. Whitby and McLaws (2004) observed hand washing compliance in 395 out of a total of 668 opportunities during the period of the current study. We therefore drew the value for hand washing compliance from the *Beta* (396, 274) distribution. McBryde et al. (2004) found transmission of MRSA to the hands of HCWs in 17 out of 129 observed patient care episodes. We therefore drew the probability of transmission from the *Beta* (18, 113) distribution.

### *A.5. MCMC algorithm to estimate the transmission parameter, $\phi$*

In order to determine the posterior probability density for the transmission parameter, $\phi$, we developed an MCMC algorithm, to explore the joint posterior distribution of the augmented data and $\phi$. The process consisted of the following steps:

(1) Determine the prior probability $\pi(\phi)$; a vague Gamma(0.001, 0.001) distribution was chosen as little was known about transmission of MRSA from HCW to patient.
(2) Draw values of $h$ and $p_{ph}$ from their respective *Beta* distributions
(3) Update the vector of latent variables. Using a Gibbs steps to update $\boldsymbol{X_p}$, $\boldsymbol{Y_p}$ and $\boldsymbol{Z}$ by sampling new values of $T_i$, using the sampling distribution given by the RHS of Expression (A.7). With each iteration, all 77 cross-transmission events were updated.
(4) Update $\phi$ using a Gibbs step as described in Section A.2 and sample from the Gamma distribution given in Expression (A.5).
(5) Perform 10 000 iterations of steps 2–4, using a "burn in" period of 5000 iterations, collecting the final 5000 values of the Markov chain for $\phi$ and $R_w$ to contribute to the posterior probability density.
(6) Repeat steps 2–5 to construct 10 Markov chains. Intra and inter chain variance tests showed very good convergence. $\widehat{R} = 1.0001$ for both $R_w$ and $\phi$ (see Gelman et al., 2004, Chapter 11.6 for discussion on convergence and $\widehat{R}$ values).

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