



Transmission dynamics of methicillin-resistant *Staphylococcus aureus* in a medical intensive care unit

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Intensive care units (ICUs) play an important role in the epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA). Although successful interventions are multi-modal, the relative efficacy of single measures remains unknown. We developed a discrete time, individual-based, stochastic mathematical model calibrated on cross-transmission observed through prospective surveillance to explore the transmission dynamics of MRSA in a medical ICU. Most input parameters were derived from locally acquired data. After fitting the model to the 46 observed cross-transmission events and performing sensitivity analysis, several screening and isolation policies were evaluated by simulating the number of cross-transmissions and isolation-days. The number of all cross-transmission events increased from 54 to 72 if only patients with a past history of MRSA colonization are screened and isolated at admission, to 75 if isolation is put in place only after the results of the admission screening become available, to 82 in the absence of admission screening and with a similar reactive isolation policy, and to 95 when no isolation policy is in place. The method used (culture or polymerase chain reaction) for admission screening had no impact on the number of cross-transmissions. Systematic regular screening during ICU stay provides no added-value, but aggressive admission screening and isolation effectively reduce the number of cross-transmissions. Critically, colonized healthcare workers may play an important role in MRSA transmission and their screening should be reinforced.

Keywords: methicillin-resistant *Staphylococcus aureus*; epidemiology; mathematical modelling

1. INTRODUCTION

Hospital-acquired infection (HAI) negatively impacts on patient outcomes and causes substantial additional resources to be deployed [1,2]. It is recognized as a major concern worldwide, and the prevention and reduction of HAI are a top priority to improve patient safety and quality of care [3,4]. Over the past two decades, methicillin-resistant *Staphylococcus aureus* (MRSA) has come to the forefront of the scene and is now endemic in many hospitals and a frequent cause of outbreaks [5–7]. Intensive care units (ICUs) play an important role in MRSA epidemiology as critically-ill patients are at higher risk of infection and are transferred on discharge to other hospital sectors, thus contributing to the spread of the micro-organism. Several interventions aiming to break the chain of transmission have proved to be effective in some

countries that have succeeded in maintaining a low MRSA prevalence, but sometimes at a high financial cost [8,9] and, possibly, with unfavourable consequences for patients [10]. Similar to other types of health-care improvement strategies, successful interventions are usually multi-modal, but the relative efficacy of single measures remains unknown [11].

The use of mathematical modelling in the field of hospital epidemiology is relatively new [12] and focuses mainly on the issues of antibiotic use and resistance [13] and vancomycin-resistant *enterococci* (VRE) and MRSA transmission [14–20]. Models for MRSA suggest several strategies for control, either alone or in combination, such as rapidly identifying carriers, isolation, promoting hand hygiene measures, increasing staffing levels, cohorting contacts between nurses and patients and restricting new admissions [15–17,21–24]. Many of these models borrow concepts from earlier work on malaria transmission [25]. However, while mass action assumptions may be successfully applied when considering a whole hospital or hospital–community interactions [19,26], the small size of the population on a single ward, especially in ICUs [26], means that

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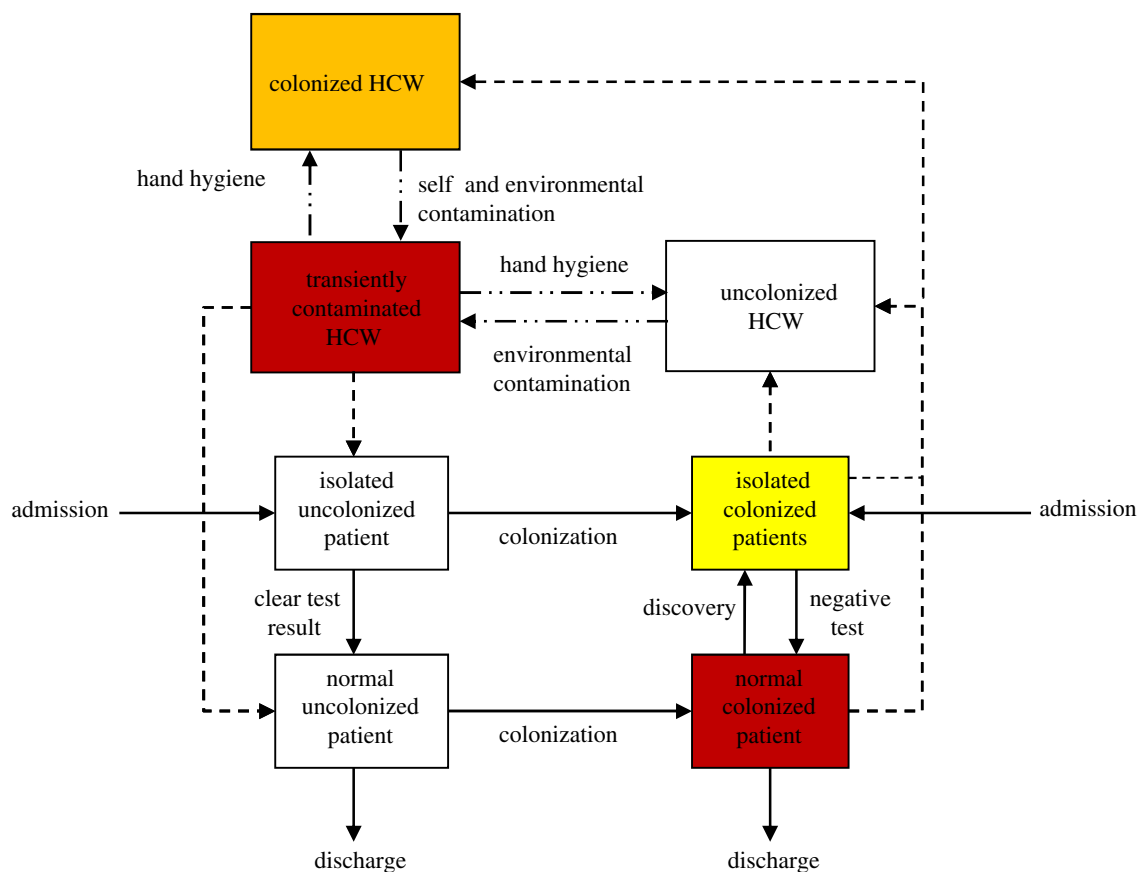


Figure 1. Dynamics of MRSA transmission between patients, healthcare workers and the environment. Solid arrows represent movement of individuals, and dashed arrows indicate transmission between HCWs and patients; red and yellow boxes are sources of contamination or colonization; the orange box shows a potential reservoir of re-contamination. Colonized patients may be released from isolation after either a false-negative test result or a true-negative result of a test sample taken before colonization. The ‘transiently contaminated HCW’ box is a convenient grouping of both colonized and non-colonized HCWs.

stochastic effects become increasingly important, especially when considering the intricacies of patient–healthcare worker (HCW) contact [27].

In the medical intensive care unit (MICU) of the University of Geneva Hospitals, Geneva, Switzerland, local surveillance data are available for highly structured populations of HCWs and patients. To reasonably capture the small populations and to take advantage of this wealth of data, we present an individual stochastic model designed to explore the transmission dynamics of MRSA in the ward. This model is used to describe the observed pattern of cross-transmission and allows us to address some potential policy scenarios relevant to the setting.

2. METHODS

2.1. Setting

The University of Geneva Hospitals is a 2000-bed tertiary healthcare facility serving a population of around 800 000 in the canton of Geneva and surrounding area. Approximately, 40 000 patients are admitted annually for a mean length of stay of 10 days. A prospective cohort study was conducted in the adult MICU from April 2004 to September 2005. All patients were systematically screened at admission for MRSA and isolated until

found to be negative for contamination [28]. Infection control procedures did not change over the 548 day study period. Specific measures for MRSA patients consisted of an admission alert system for those with known previous carriage—hereinafter referred to as prior-colonized patients—implementation of contact precautions, topical decolonization and regular reporting of results from surveillance [29–32]. Using an alcohol-based handrub solution for hand hygiene was also promoted as part of a longstanding, hospital-wide programme throughout the study period [11,33].

2.2. Transmission dynamics and assumptions

The MRSA dynamic transmission process was analysed using a discrete time, individual-based, stochastic model (figure 1). All patients are immediately screened at admission and pre-emptively placed in contact isolation until a negative test result is obtained. We assume that isolation is not fully effective and that transmission could occur despite isolation being in place. We assume also that the sensitivity of screening, whether by polymerase chain reaction (PCR) or clinical culture, is below 1, thus resulting in isolation being lifted for some MRSA-positive patients or failure to isolate an MRSA-positive patient. Once colonized, it is assumed that patients remain so, regardless of any decolonization

Table 1. Model input parameters. (HCWs, healthcare workers; ICU, intensive care unit; PCR, polymerase chain reaction; SSMI, Société Suisse de Médecine Intensive.)

parameters	value	source
number of beds	max. 20	hospital data
admission rate, discharge rate, length of ICU stay	derived from hospital database	hospital data
probability of being an prior-colonized patient	0.0877	surveillance
probability of being a non-prior-colonized patient at admission	0.9123	surveillance
probability of colonization at admission among non-prior-colonized patients	0.0721	surveillance
probability of colonization at admission among prior-colonized patients	0.57	surveillance
frequency of subsequent PCR screening during ICU stay	once a week	policy
probability of discharge screening	1	policy
frequency of culture (category SSMI IB-II)	1 test per day or every other day	surveillance
time between PCR and result in hours (mean, s.d.)	19.6 (7.3)	survey [24]
time between culture and result in hours (mean, s.d.)	97.6 (29.4)	survey [24]
probability of hand hygiene before patient contact	0.56 (0.28)	survey
probability of hand hygiene after patient contact	0.69 (0.21)	survey
number of ICU nurses (day, evening and night shift) (mean, s.d.)	13.5 (1.105) 10.1 (0.539) 9.0 (0.593)	hospital data
number of ICU nursing assistants (day, evening and night shift) (mean, s.d.)	4.9 (0.934) 2.3 (0.531) 1.0 (0.100)	hospital data
number of ICU physicians per shift (day/night) shift	5/5	hospital data
number of non-ICU staff (day, evening and night shift)	9/2/2	survey
sensitivity of PCR test ^a	0.95	assumption
sensitivity of culture (when used for screening) ^a	0.8	assumption
sensitivity of culture (when used for clinical specimen) ^a	0.2	assumption
efficacy of hand hygiene ^a	0.8	literature [31]
efficacy of isolation ^a	0.7	literature [21,37]
proportion of intermittently colonized HCWs ^a	0.041	literature [32–36]
probability that contact with patient was sufficient to <i>contaminate</i> HCW's hands, P_{PH} ^a	0.15	literature [15,31]
probability that contact with HCW was sufficient to <i>colonize</i> patient, P_{HP}	fitted to data	
probability of contamination from environment to HCWs' hands, P_E	fitted to data	
probability of hand contamination from HCW themselves, given that the HCW is intermittently colonized with MRSA, P_R	fitted to data	

^aParameters submitted to sensitivity analysis.

attempt, while on the ward, as the length of patient stay is typically much less than the decolonization timescale. Upon entry to the ward, the bed allocated to the patient is assumed to be MRSA-free. Thus, as patients admitted to the ICU remain bedridden, MRSA-negative patients can become colonized only through direct contact with a HCW harbouring MRSA on his/her hands and not through the environment, other patients or (non-HCW) visitors.

Four categories of HCW are in contact with patients in this setting: nurses; nursing assistants; physicians and other staff, such as physiotherapists, X-ray technicians, etc. A HCW's hands can be contaminated either through contact with a colonized patient, environmental contamination or self-contamination because he/she is colonized. Hand hygiene is effective in removing MRSA from hands, although not 100 per cent [34]. For HCWs and patients, no attempt was made to model the individual extent of contamination or colonization. Patient severity of illness and the ward staffing level determine the number of contacts with each HCW category. These contact

rates were obtained through a contact study on the ward. HCW-mediated transmission of MRSA between patients is influenced by the efficacy of, and compliance with, hand hygiene practices. It is assumed that HCWs should perform hand hygiene immediately before and after patient contact, according to standard recommendations [35,36].

2.3. Data and parameters

Model parameters were derived from hospital data unless specified otherwise (table 1) and the processes they specify are described below.

2.3.1. Methicillin-resistant *Staphylococcus aureus* surveillance

The admission of MRSA-positive patients among overall admissions can be modelled by a binomial distribution. In total, 8.77 per cent of all admissions are registered as having a previous history of MRSA colonization: the so-called prior-colonized patients [29,31,32]; of these, 57

Table 2. Observed pattern of cross-transmission events during the surveillance period.

	all data	Monday	other days
number of observed cross-transmissions over study period	46	23	23
mean daily rate of cross-transmission events	0.084	0.295	0.049
variance of daily rate of cross-transmission events	0.103	0.392	0.047
<i>p</i> -value of fit to maximum-likelihood estimate Poisson distribution	0.033	0.18	0.9
<i>p</i> -value of fit to maximum-likelihood estimate negative binomial distribution	0.98	0.94	—
days with zero cross-transmission events	508	61	447
days with one cross-transmission event	35	12	23
days with two cross-transmission events	4	4	0
days with three cross-transmission events	1	1	0

per cent are found to be colonized at admission screening. Of the remaining admissions, 7.2 per cent are found to be colonized at admission.

All patients were screened specifically for MRSA within 24 h of admission, upon discharge and, if present, each Monday. All screening at discharge was by conventional culture, as was all admission screening of patients with a known history of MRSA carriage [28]. The sensitivity of such a test was assumed to be 0.8; all other screening was by PCR with a sensitivity of 0.95. According to the patient's condition, clinical samples were taken either daily or every other day and cultured. As these samples are taken from a single body site for clinical reasons and not specifically for MRSA detection, the sensitivity here is lower and assumed to be 0.2. Results of PCR and culture tests were available within 24 h and 4 days, respectively [28].

MRSA cross-transmission was deemed to have occurred in the ICU when patients who had tested negative at admission later tested positive during their stay or on discharge from the ward. In total, 46 MRSA cross-transmission events were observed in the ICU during the 18 month study period (giving a rate of 5.77 events per 1000 patient-days at-risk (95% confidence interval (CI), 4.24–7.68)). The mean daily rate of (observed) cross-transmissions on the ward was 0.084 (46/548) with a variance of 0.10 (table 2). The date of the individual observation is when the positively tested sample was taken and not the date of the cross-transmission event itself. For this reason, a large number of cases [38] were identified on Mondays owing to the weekly procedure of PCR testing of inpatients. These surveillance data are used to calibrate the model prior to scenario testing.

2.3.2. Flow of patients and bed occupancy

The MICU has a total capacity of 20 beds; occupancy is typically around 15 beds and is only very rarely more than 18 beds. Analysis suggested that admission may be viewed as a Poisson event with expected admissions in a given hour dependent on bed occupancy and time of day (for example, admission rates are almost halved when 17 or more beds are occupied than when 14 or fewer are). Over the study period, 2559 patients were admitted for a mean length of stay of 3.8 days (standard deviation (s.d.), 4.6 days). The length of stay of each case did not conform to a clear theoretical distribution and, for this reason, each case has a length of stay directly sampled from the administrative database depending on the time of day they entered to the nearest 30 min. These processes replicate the observed bed occupancy and discharge pattern much more accurately than a simpler approach and so are used in the model.

2.3.3. Working pattern and staffing level

The number of nurses and nursing assistants for each shift was randomly sampled from a normal distribution with the appropriate means and s.d. derived from the administrative database (table 1). Numbers were constant for physicians and extra-ICU staff (consultants, technicians, etc.). Following ICU policy, a moderately ill patient shares a nurse with another patient, while a severely ill patient will, if resources on the shift permit, be assigned a dedicated nurse. This staff-patient 'cohorting' was kept as strict as possible in the model, although, true to reality, occasionally staffing levels were not sufficient to allow such a contact pattern (particularly on night shifts). Each team of physicians cared for half of the patient population with little crossover. Nursing assistants and extra-ICU staff could have contacts with any patient.

2.3.4. Contact study and mixing pattern

A survey was performed on 17 randomly selected patients to estimate the number of contacts between patients and HCWs over a 24 h period. A contact was defined as an opportunity for MRSA cross-transmission between a HCW and a patient, i.e. each time a HCW approached and touched a patient and/or the surrounding environment, regardless of the type and duration of care. The type of HCW with whom the patient had contact was recorded and whether a dedicated nurse was assigned to only this patient, or if she/he had contact also with other patients. The number of contacts per patient is stratified by shift, severity of illness and HCW category and this parametrizes the model (table 3). A nurse may be assigned to a patient at the start of his/her shift and/or when there is a new admission to the ward.

2.3.5. Compliance with hand hygiene recommendations

Compliance probabilities were derived from an observational survey in the ICU according to a previously described methodology [11,37] during which we observed 557 situations where hand hygiene would have been recommended during 54 20-min observation periods. Overall compliance with hand hygiene before and after

Table 3. Contact rate and mixing pattern between healthcare workers and patients.

	day shift		evening shift		night shift	
	moderately ill	severely ill	moderately ill	severely ill	moderately ill	severely ill
total number of contacts	13	21	13	13	6	8
assigned nurse	5	11	7	7	4	5
other nurse	2	3	2	1	0	0
nursing assistant	2	2	1	2	1	1
physician	2	3	1	2	1	1
other healthcare workers	2	2	2	1	0	1

Table 4. Summary of statistics of compliance with hand hygiene recommendations before and after patient contact according to healthcare worker category. (Numbers are means (s.d.)).

	before patient contact	after patient contact
nurses	0.55 (0.29)	0.74 (0.26)
physicians	0.68 (0.47)	0.72 (0.43)
nursing assistants	0.82 (0.34)	0.77 (0.42)
other healthcare workers	0.58 (0.49)	0.6 (0.55)

patient contact was 0.61 and 0.73, respectively (table 4). Compliance behaviour is polarized within each HCW category, with some proportions either never complying or always complying. Thus, in the model, the compliance likelihood for each HCW was sampled from the raw data at the beginning of his/her shift, rather than modelled by a theoretical distribution.

2.3.6. Transmission rates and probabilities

The probability that a contact with a colonized patient was sufficient to contaminate a HCW's hand with MRSA ($P_{PH} = 0.152$) was taken from the literature [12,34] and based on the observed number of HCWs exhibiting contamination following contact with a known colonized patient. *A priori*, there is no reason to expect the probability of colonization of a patient by a contaminated HCW (P_{HP}) to be the same as P_{PH} and since no (non-modelled) data were found in the literature to support its parametrization, P_{HP} is a free parameter in our model. HCWs may also become contaminated through interaction with the ward environment. The probability of contamination from the environment to HCWs (P_E) over 1 h is unknown and highly dependent on the setting itself. This parameter is therefore also a free parameter in our model, although it is assumed to be constant over the study period.

We inferred from the literature that the probability of a HCW suffering nasal MRSA carriage was 4.1 per cent (104 studies; 95% CI, 0.3–7.9%) [39–44]. Consequently, such a HCW's hands were likely to be self-contaminated with some probability per hour P_R following decontamination through hand hygiene. *A priori*, it is reasonable to assume that this self-contamination is more likely than environmental transfer so $P_R > P_E$. For convenience, we refer to environmental

contamination and this self-contamination collectively as indirect sources of contamination, as opposed to the direct contamination following contact with patients. In addition, Harbarth *et al.* [32] found that 6.4 per cent of HCWs were contaminated with MRSA when hands were sampled. HCW contamination is likely to be much more setting-dependent than colonization owing to the transitory nature of the former. As this value has been elicited from a smaller number of studies (24, and not the earlier-mentioned 104) and no range is provided, we have used this as an indicative carriage rate for comparison, rather than a value to fit the model.

2.4. Model structure

Modelled HCWs have five state variables: HCW category, hand hygiene compliance probability before contact, compliance probability after contact, colonization status and hand contamination status. The category of a HCW determines the contact pattern with patients and the number in each category varies by shift. The contamination status changes dynamically through contact with patients and the environment, and through self-contamination, whereas the other variables are determined at the start of a shift.

Each occupied bed has six state variables: current status (occupied by a non-colonized, but isolated patient; colonized and isolated; non-colonized and not isolated; colonized, but not isolated; or empty); currently allocated nurse; time remaining to discharge; time to next MRSA screening test; number of tests performed so far on the patient and the care requirements. Furthermore, each MRSA test performed on a bed has three state variables: time to the next result becoming available, status of the bed at the time of the test and the type of test performed. The type of test performed implies a delay between testing and the result becoming available and carries with it a particular sensitivity. Each simulation is seeded with bed occupancy derived from the hospital's administrative database for the first study day.

2.5. Model fitting

As mentioned above, the model has three free parameters: P_{HP} , P_E and P_R . We use an adaptive grid search over the three-dimensional parameter space to determine candidate good descriptors. For each sampled parameter set, the observed frequencies of

cross-transmission events are compared with the empirical expected frequencies simulated from the model (average of $n=200$ realizations) through an exact multi-nomial test for both sets of frequencies provided by the surveillance and shown as cross-transmission events occurring on Mondays and those on other days. Parameter sets for which simulations result in $p > 0.1$ in comparison with *both* sets of the observed frequencies are deemed good descriptors of the surveillance data. Those for which $p < 0.05$ when compared with *at least one* of the frequencies are rejected as plausible descriptors of the data; other parameter sets are described as weak descriptors of the data. In regions of parameter space where good descriptors are found, the resolution of sampling is greater than in areas where all ensembles are rejected as weak descriptors. The chosen strategy was to fix P_{HP} and then eventually resolve P_R to two decimal places (d.p.) and P_E to three d.p. (noting that P_R typically acts on only 4.1 per cent of the HCWs and so should be an order of magnitude greater than P_E). Valid fits to the data might exist at greater resolutions but such fidelity may effectively be over-fitting the model given uncertainty in other parameters. Sensitivity to uncertain parameters is considered and shown in the accompanying electronic supplementary material.

2.6. Scenario analysis

The base-case scenario was the infection control policy in place at the time of the study; in brief, systematic admission screening, systematic isolation at admission until found to be negative, and weekly and discharge systematic screening. Alternative strategies for MRSA screening and transmission control can be investigated through the model once it is calibrated to the data. In particular, a number of scenarios are investigated that involve combinations of delaying isolation until receipt of admission screening test results, changing admission screening policies, changing the screening policy during stay and at discharge, and removal of cohorting nurses to patients. Differences in the number of cross-transmission events and study days under isolation will be reviewed.

3. RESULTS

Table 2 shows the summary statistics of the surveillance data. A χ -square goodness-of-fit test showed that the sample of MRSA cross-transmission events was significantly different from that expected from a Poisson process given the sample mean at the 5 per cent level ($p=0.033$), with the observed transmission events exhibiting significant evidence of overdispersion [45]. Considering the weekly PCR testing, data are split by day of the week and this apparent overdispersion is caused by an aggregation of cases being reported on Mondays. The other days see transmission events in a Poisson manner ($p=0.9$) and, while the Monday pattern of events shows some evidence of a Poisson process ($p=0.18$), a Poisson-gamma model (otherwise called a negative binomial) is a better representation of the Monday observations ($p=0.94$).

3.1. Model fitting

Fixing all parameters listed in table 1, other than the three unknown parameters impacting on the transmission mechanisms, P_{HP} , P_E and P_R , leads to the conclusion that as P_{HP} becomes stronger, the indirect contamination route must decrease to accommodate the same number of cross-transmissions. Indicative parametrizations are shown in table 5 and discussed in more detail below.

The parameters that best describe the observed pattern of cross-transmission events imply that patient colonization is as likely as HCW contamination at contact ($P_{HP} \sim P_{PH}$), and that the probability of HCW indirect contamination in any given hour is rare. This is because the model displays overdispersion in this area of parameter space (table 5). In this situation, the MRSA carriage rate on hands among HCWs is consistently less than 1 per cent compared with 6.4 per cent of previously reported [32].

In the situation, where P_{HP} is less than a quarter of P_{PH} , the evidence from the model indicates at best only a weak description of the observed data. In the extreme and unrealistic situation that all HCWs are permanently contaminated, then $P_{HP}=0.0008$, the p -value associated with comparison of the Monday events is 0.065, and the p -value associated with the remaining days is 0.05. Therefore, this parametrization fails our criteria for even a weak description of the data and the 88 per cent contamination carriage rate is also an order of magnitude different from the literature.

Assuming that only the 4.1 per cent of HCWs colonized are permanently contaminated, it can be observed that the likelihood of the remaining HCWs being transiently contaminated decreases ($P_E=0.022$), but $P_{HP}=0.01$ has increased. The p -values associated with the Monday and non-Monday observations (0.085 and 0.085, respectively) indicate a weak fit, although the prevalence of HCW hand contamination is now 7.3 per cent. Assuming that the intermittently colonized HCWs are no more likely than their colleagues to be contaminated, and fixing $P_{HP}=0.01$, means that $P_E=0.049$, but contamination prevalence remains about 8 per cent and the p -values (0.094 and 0.071) provide no strong evidence to accept such a scenario. The parametrization of $P_{HP}=0.01$ is similar to other model-derived estimates [15]. However, it is important to note that the fitting was derived with a different model paradigm and so a simple translation may be misleading. Increasing $P_{HP}=0.012$ provides a contamination prevalence matching that reported in the literature, but no discernable improvement can be observed for the indicative coupling of $P_E=0.015$ and $P_R=1$ in the p -values to enable strong acceptance of the scenario as describing the observations.

As P_{HP} increases, the maximum p -value considering the Monday events improves. When considering $P_{HP}=0.05$, while the p -values of the observed pattern of events are not as good as those achieved for larger values of P_{HP} , they are better than those with smaller values and conform to our specified criteria for sound evidence of describing the transmission dynamics ($p > 0.1$ for both frequency comparisons). However,

Table 5. Indication of the most likely coupling of parameters P_E and P_R , given a value of P_{HP} that reproduce surveillance data. (HCWs, healthcare workers.)

P_{HP}	P_E	P_R	p -value (multi-nominal exact test) associated with non-Monday cross-transmission events	p -value (multi-nominal exact test) associated with Monday cross-transmission events	mean number of cross-transmission events reported on Mondays	mean number of cross-transmission events reported on other days	mean number of cross-transmission events reported in total	mean number of cross-transmission events	variance of cross-transmission events	mean number of unreported cases	Mean percentage of HCWs with hand contamination
0.15	0	0.01	0.55	0.13	15.1	29	48.8	44.1	106.8	4.7	0.5
0.05	0	0.19	0.22	0.13	17.2	31.3	53.6	48.5	52.5	5.1	1.4
0.05	0.007	0	0.1	0.13	17.9	33.6	57.1	51.5	73	5.6	1.5
0.012	0.015	1	0.042	0.086	18.8	36	61	54.8	51.6	6.1	6.3
0.01	0.022	1	0.085	0.085	18.1	34.1	58.1	52.2	58.9	5.9	7.3
0.01	0.049	0	0.071	0.094	18.7	34.4	58.8	53.1	50.7	5.7	7.7
0.0008	1	1	0.05	0.065	18.3	35.4	60	53.7	41	6.3	88.4

the parametrization in table 5 with $P_E = 0.007$ and $P_R = 0$ would require that colonized HCWs are no more likely to be contaminated than other HCWs.

Fixing $P_{HP} = 0.05$ and setting $P_E = 0$ leads to similar goodness-of-fit results as described above. Figure 2 shows the changes in p -value and observed cross-transmission events as P_R is varied. When $P_R = 0.13$, the model very clearly replicates the dynamics of the 23 events reported on days other than Mondays ($p = 0.90$); however, on average, only 14 are seen on a Monday ($p = 0.004$). Roughly doubling P_R to 0.35 suggests that the Monday surveillance consistently reports 23 events ($p \sim 0.35$), but now the non-Monday events report about 39 events ($p = 0.01$). While both these situations caused us to reject the parameter sets as valid descriptors of the observed data given our acceptance criteria, values of P_R between these ranges provide a compromise such that when $P_R = 0.19$, the p -value for both surveillance streams is greater than 0.1 ($p = 0.13$ for non-Monday; $p = 0.22$ for Monday, although similar behaviour is observed for values of P_R from 0.18 to 0.21). Such a value of P_R suggests that the probability of self-recontamination over an 8 h shift is around 0.87 and shows that a colonized HCW is likely to recontaminate him/herself at least once during a shift.

Given a parametrization of the model with $P_{HP} = 0.05$, $P_E = 0$ and $P_R = 0.19$, figure 3 shows the course of each patient that suffered a cross-transmission event on the MICU. The simulation that resulted in this distribution of events was the single realization that best matched the surveillance data. It should be recalled that patients are never decolonized while on the ward, but they are placed back under isolation following positive test results. Of note, many cases leave the ward soon after colonization (15 out of 50 leave within 24 h of colonization), but some stay for a substantial period of time, albeit under isolation. In this simulation, 19 patients of 46 were identified by discharge screening (as well as the four that were never identified) and so never returned to isolation conditions.

3.2. Scenario analysis

Assuming that the derived parametrization of $P_{HP} = 0.05$, $P_E = 0$ and $P_R = 0.19$ is representative of the dynamics on the ward enables the evaluation of various policy scenarios. Table 6 shows the results from the model of changes to certain protocols on the ICU. For the PCR and culture test sensitivity chosen here, it can be observed that about 5.1 cross-transmissions are missed by the existing surveillance protocols. Furthermore, for these parameters, it can be seen that about 14.9 per cent of beds were occupied by colonized patients, but 89 per cent of these were under isolation conditions, thus suggesting that severe outbreaks were effectively curtailed. By contrast, 65 per cent of beds under isolation were MRSA-free. Of the 53.6 cross-transmission events calculated by the model, 6.4 per cent occurred under isolation. We note that the variance of the reported cross-transmission events resembles the variance of the actual events manifest in the surveillance data.

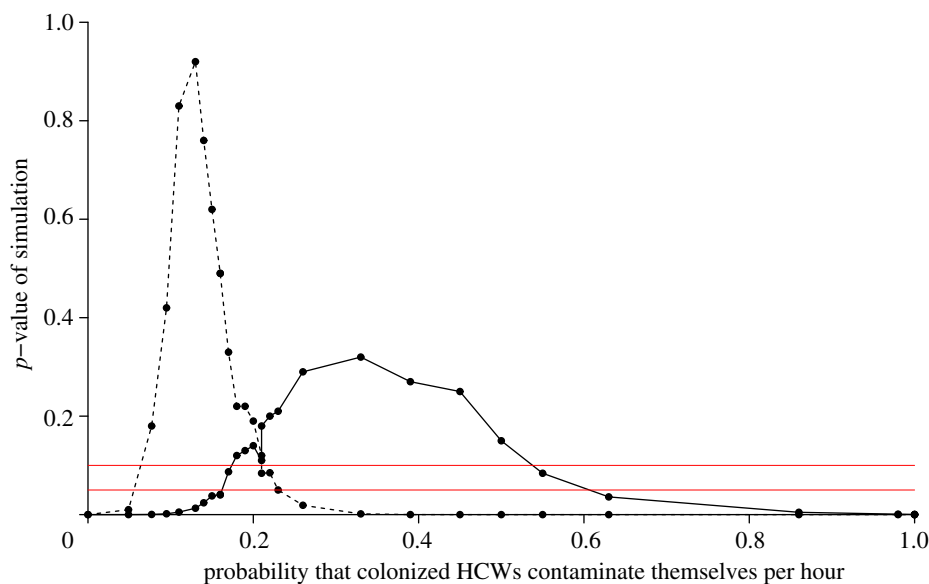


Figure 2. p -value arising from simulations with $P_{HP} = 0.05$, $P_E = 0$ for values of P_R , given all other parameters fixed. Red lines highlight p -values of 0.05 and 0.1; the solid line shows the p -values associated with simulations describing the Monday data and the dashed line the equivalent for non-Monday data.

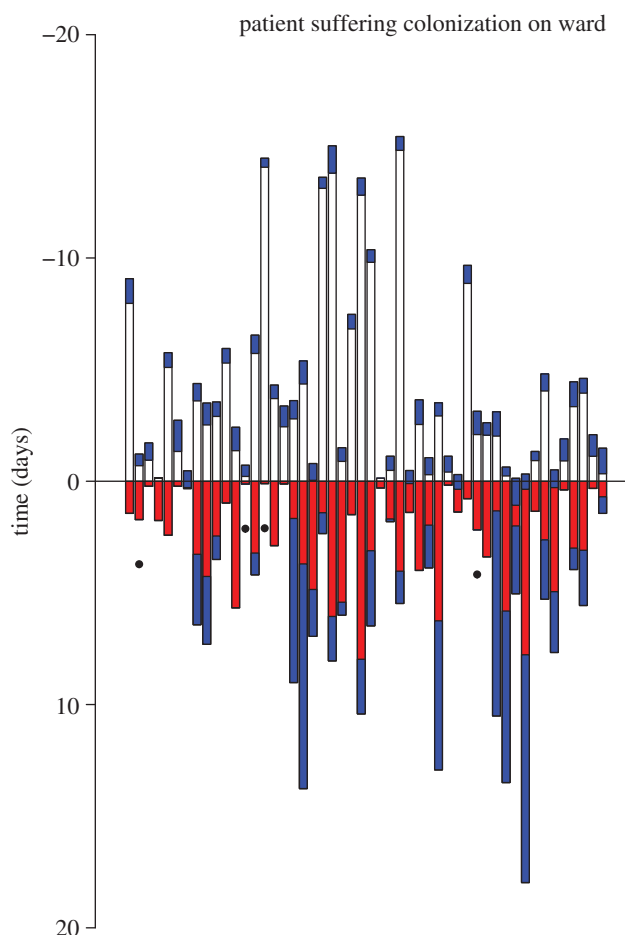


Figure 3. Patients suffering cross-transmission events arising from the 'best-fit' realization of the model given a parametrization of $P_{HP} = 0.05$, $P_E = 0$ and $P_R = 0.19$. Blue colouring indicates that the patient is under isolation; white indicates that the patient has been moved to non-isolation nursing conditions; and red colour indicates that they are colonized and not isolated. The length of each bar reflects the time (in days) spent in each state; a black dot indicates that the case was never identified by surveillance.

Switching from PCR-based weekly and admission screening of individuals who were not prior-colonized patients to culture testing, but otherwise keeping the admission isolation policy in place, had almost no discernable impact on the pattern of cross-transmission events. Removing the weekly PCR screening protocol would appear to increase the total cross-transmission events by 1 (to 55.3) and reduce the number reported by about 1, resulting in two extra missing events. Most transmission events are now being identified by discharge culture screening. While the equivalent number of patient-days spent colonized remains unchanged (15% of total), about 0.7 per cent more patient-days are spent out of isolation than in the existing situation. As expected, further removal of discharge screening has no impact on cross-transmission events, but drastically reduces the events observed on average (20.7 rather than 48.5). Thus, changing policy with respect to discharge or weekly screening, whether complete removal or change to culture testing where relevant, would appear to have a marginal impact on the total cross-transmission burden on the ward.

Changes to entry screening and isolation policy have a more profound impact on cross-transmission. Screening only patients with a previous history or suspicion of MRSA colonization and isolating until negative test results are available, but not isolating other patients until MRSA-positive clinical test results, causes 72.2 events, 18.6 more than in the existing situation. The equivalent of 11.6 per cent of patient-days was spent in isolation, a major reduction compared with the 37.6 per cent of patient-days arising from current policy according to the model. Isolating patients only when the culture test returns positive results in 21.8 excess cross-transmission events compared with the existing policy and is broadly similar to the situation of not screening patients at admission. In the extreme situation of having no screening policies and isolating only when the comparatively insensitive clinical culture

Table 6. Summary measures resulting from scenario analysis.

isolation strategy	admission policy	other screening policies	mean total cross-transmission events	percentage of colonization events occurring under isolation	variance of total cross-transmission events	mean observed cross-transmission events	variance of observed cross-transmission events	mean number of unobserved events	mean percentage of HCWs contaminated	percentage of patient-days spent colonized and isolated	percentage of patient-days spent colonized and not isolated	percentage of patient-days spent uncolonized and not isolated
existing procedures/protocols	existing procedures/protocols	existing procedures/protocols	53.6	6.4	56.1	48.5	52.5	5.1	1.4	13.3	1.6	61
isolation unchanged	all admission screening by culture test rather than PCR	all screening by culture tests rather than PCR	54.3	6.2	53.9	48.7	44.2	5.5	1.5	13.3	1.8	61
isolation unchanged	admission screening unchanged	no weekly PCR screening	55.3	6.8	63.2	47.9	54.4	7.4	1.5	12.6	2.5	60.6
isolation unchanged	admission screening unchanged	no weekly screening, no discharge screening	54.6	6.6	60.1	20.7	22.5	34	1.5	12.6	2.5	60.4
isolation at admission of patients with previous MRSA history	admission screening of only patients with previous MRSA history	policy unchanged	72.2	0.3	74.1	57.6	59.4	14.6	1.7	9.2	6.4	82.4
delay isolation until receipt of first MRSA-positive screening test	admission screening unchanged	policy unchanged	75.4	0	96.6	67.2	79.7	8.2	1.8	8.9	6.9	84.5

(Continued.)

Table 6. (*Continued.*)

isolation strategy	admission policy	other screening policies	mean total cross-transmission events	percentage of colonization events occurring under isolation	variance of total cross-transmission events	mean cross-transmission events	variance of observed cross-transmission events	mean number of unobserved events	mean percentage of HCWs contaminated	percentage of patient-days spent colonized and isolated	percentage of patient-days spent uncolonized and not isolated	percentage of patient-days spent colonized and not isolated	percentage of patient-days spent uncolonized and not isolated
delay isolation until receipt of first MRSA-positive screening test	admission screening of only patients with previous MRSA history	policy unchanged	81.1	0	105.6	64.4	72	16.7	1.9	6.6	0	9.6	84.2
delay isolation until receipt of first MRSA-positive screening test	no admission screening	policy unchanged	82.2	0	80.9	64.8	63.1	17.4	2	6.5	0	9.9	83.8
delay isolation until receipt of first MRSA-positive screening test	no admission screening	no weekly screening; no discharge screening	86	0	105.5	28.4	33.4	57.6	2.2	3	0	13.3	83.9
no isolation policy	admission screening unchanged	policy unchanged	95.3	0	131	85.2	119.6	10.1	2.3	0	0	17	83.1
isolation policy unchanged	admission screening unchanged	existing procedures and protocols, but attempts to cohort staff to patients have ceased	61.4	8.5	75.1	55.4	66.3	6	1.4	13.6	24.3	1.8	60.5

test detects an MRSA-positive patient, we observe 86 events, although only 3 per cent of patient-days are spent in isolation.

Removing isolation completely creates nearly 95.3 cross-transmissions in total (although only 85.2 would be observed) during the equivalent study window, effectively doubling the number of transmission events observed in patients. Any policy decision to change the isolation procedure will thus increase the cross-transmission events. Removal of the cohorting of nurses to particular patients results in a 15 per cent increase in cross-transmission events.

4. DISCUSSION

This study provides important insight into the dynamics of MRSA transmission in intensive care and provides sound evidence to support aggressive screening and isolation of all patients at admission. We have shown stable and consistent results for an individual-based model of MRSA transmission in an MICU setting and were able to generate a class of simulated results that consistently reconstruct the observed data. In summary, broad areas of parameter space achieve some evidence of the model describing the observed data, given the fixed measured/observed parameters.

The source and plausibility of the parameter values are of crucial importance in modelling studies. We believe our study is unique and contrasts with others in the following ways. First, the model was calibrated to high-quality data on MRSA cross-transmission obtained through intensive prospective individual surveillance. Only a few other studies on MRSA transmission have used locally observed surveillance data in their models [15,46–48]. In particular, it is critical to note that discharge screening was systematically performed in this setting (note that without such screening only about 40% of cross-transmission events are observed). Consequently, models calibrated to data with no discharge screening or post-discharge surveillance could require some careful interpretation. Furthermore, rather than assume transmission parameters, we have been able to calibrate these to our data. Of note, the literature shows extreme variation from one study to another [17,26,37,47] where different methodologies are used and different settings examined.

Second, the vast majority of parameters were extracted either from the local administrative database, surveillance or specific surveys. Indeed, assumptions were made on only three parameters (sensitivity of clinical culture, screening culture, and PCR), and the other four parameters not locally measured were derived from the literature. Critically, and in contrast to other studies [26,46], we did not assume a homogeneous mixing pattern between patients and HCWs, but used survey data to model the contact rate, which were similar to those observed by Grundman [12]. This probably has a major impact on the results as severely ill patients are more likely to be colonized with MRSA compared with those moderately ill patients and have more contacts with HCWs, particularly with their dedicated nurse. Compliance with hand hygiene differs across

HCW categories and tends to be lower before patient contact than after, although this might not be extrapolated from experiences on other types of ward [11,33]. For this reason, observational studies in the setting itself are essential for meaningful data and models [12]. In addition, although the efficacy of hand hygiene protocols are thought to be important factors determining MRSA transmission, many others assumed hand hygiene efficacy to be 100 per cent [17,26]. Of note, the fact that a large number of input parameters were locally acquired increases the internal validity of the study; however, the results cannot be inferred to other hospital settings, such as a surgical ICU, and should be inferred to an international context with caution.

Whether patients admitted to the ICU should be screened, the type of screening scheme, and whether they should be isolated on admission, remain highly controversial issues. This study allowed the investigation and quantification of the effect of various screening and isolation policies on cross-transmission and the use of additional bed-days for isolation. Importantly, the lowest number of predicted cross-transmissions occurred under the current policy (systematic screening and isolation at admission of all patients). Three alternative strategies had no impact on the number of cross-transmissions occurring in the ICU: culture instead of PCR for admission screening, removal of weekly screening, and removal of discharge screening. The latter might be expected as these strategies exist to monitor trends in cross-transmission events and so inform the need for further intervention, rather than directly stop such events. Only a few cross-transmissions went unobserved when removing weekly screening because the average length of ICU stay is short and, more importantly, because the test frequency is very high when combined with admission screening and cultures performed on clinical grounds. Approximately 800 weekly screening tests performed per year could be eliminated, provided that other elements of the policy are kept in place and represent a real saving of both human and economic resources. These findings support a study by Perenevich *et al.* that demonstrated the benefit of admission isolation, active surveillance culture and contact precautions for colonized patients to reduce the spread of VRE in intensive care [49,50]. Absence of discharge screening did not result in an increased number of cross-transmission events in the ICU or an increase in the number of patient-days under isolation. However, screening upon discharge from the ICU will provide a more accurate figure of the number of cross-transmission events, which was important to calibrate our model. In addition, discharge screening identifies additional patients colonized with MRSA who may represent an important burden for the wards receiving these patients after ICU stay [51].

A substantial proportion of MICU patients are colonized or infected with MRSA, many of whom have no previous history of MRSA carriage. As the highest frequency of contacts between HCWs and patients (and opportunities for cross-transmission) is around admission time to the MICU, modification of the admission screening and isolation policy might be expected to have a profound impact on cross-transmission. In the

model, the number of cross-transmission increases by almost 40 per cent if only prior-colonized patients (i.e. those with known previous carriage) are screened and isolated, by about 50 per cent if isolation is put in place only after the results of the admission screening become available, and by over 60 per cent in the absence of admission screening and isolation.

The role of the environment in MRSA transmission has been a subject of debate for decades. In this setting, a HCW's hand can become contaminated directly by colonized patients, by the environment, or through self-contamination, but the impact of the latter two transmission parameters are unknown [35]. We recognize that our model does not take into account the fact that patients can acquire MRSA directly from the environment (i.e. without staff hands as an intermediate carrier). In a recently published study [21], commonly touched environmental surfaces around patients were as likely to be contaminated with MRSA as patients' skin sites. It is clear that patients colonized or infected with MRSA are likely to both spread MRSA around and acquire it from the environment. To the best of our knowledge, no study in the literature has quantified the phenomenon of direct cross-transmission and self-contamination between the patient and his/her close environment. Similarly, the role of environmental cleaning in the control of MRSA still needs to be further defined using appropriately conducted studies controlling for environmental contamination and staff compliance with hand hygiene [35,52]. Overall, indirect transmission seems to play a major role as it accounts for five-sixths of cross-transmissions in our model. However, with 4.1 per cent of ICU staff colonized and likely to self-contaminate over a shift, environmental transfer would appear negligible. Our findings have some implications for MRSA control and suggest that a more systematic recourse to HCW screening, usually performed only in the case of outbreak control, together with proven effective decontamination strategies would have a significant impact on endemic MRSA transmission. A practical implication for future research is that the contemporary measurement of environmental contamination, patient carriage status and HCW colonization and hand contamination while working on wards deserve more attention and systematic studies. It is important to recall that if the prevalence of HCW colonization was lower on this MICU than reported in the literature, the role of the environment would consequently be more important.

Mathematical modelling is a useful and underused tool in infection control and hospital epidemiology. Our work highlights the importance of aggressive infection control measures at ICU admission and questions the importance of the environment in the dynamic of MRSA transmission in this setting [21,52]. The prevalence of colonization among HCWs should be more systematically assessed to better understand its role in MRSA dynamics and to help tailor infection control measures accordingly.

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