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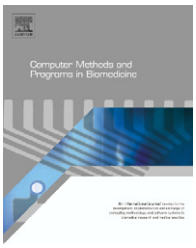

Modelling of Healthcare Associated Infections: A study on the dynamics of pathogen transmission by using an individual-based approach

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ABSTRACT

Prevention and control of Healthcare Associated Infections (HAIs) has become a high priority for most healthcare organizations. Mathematical models can provide insights into the dynamics of nosocomial infections and help to evaluate the effect of infection control measures. The model presented in this paper adopts an individual-based and stochastic approach to investigate MRSA outbreaks in a hospital ward. A computer simulation was implemented to analyze the dynamics of the system associated with the spread of the infection and to carry out studies on space and personnel management. This study suggests that a strict spatial cohorting might be ineffective, if it is not combined with personnel cohorting.

1. Introduction

Healthcare Associated Infections (HAIs) are infections that are acquired in hospitals or as a result of healthcare interventions. HAI outbreaks can cause severe and costly disruption to services. Thus the prevention and control of HAIs has become a high priority for most healthcare organizations. In particular, hospitals worldwide are increasingly concerned by methicillin-resistant *Staphylococcus aureus* (MRSA). In many countries, recent decades have seen a rapid increase in the incidence and geographical range of MRSA infections [1–3].

Although various studies of HAIs have been carried out, the exact mechanism of pathogen transmission is still not fully understood. In the case of MRSA, the most likely mode of spread is by indirect transmission via a health-care worker acting as a 'transient carrier' and indirect acquisition by contact with a contaminated environment [3–8]. Several studies provide evidence that *S. aureus* is present in the environment or in the surrounding air and, as a result, both vehicle-borne and airborne transmission might also happen [9–12].

Outbreaks are usually contained with a package of infection control measures, which may include performing active surveillance cultures to identify colonized patients, improving hand hygiene compliance, contact-based infection control, barrier precaution policies, effective staff management, antibiotic policies, and, last but not least, education [2,13,14].

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2. HAI modelling

In the last century, a variety of mathematical models have been developed in order to improve understanding of epidemiology of infectious diseases [15–17]. However, their application to nosocomial epidemiology has been rather recent (for reviews of HAI modelling see [2,14,18,19]). After initial HAI studies based on a deterministic approach, almost all research groups have started to apply a stochastic approach to the HAI problem. In HAI modelling, a stochastic approach is desirable for the following reasons [16,20,21]: (a) the infection transmission is a discrete and random event; (b) the individuals are heterogeneous; (c) the population is small.

2.1. *The state variable approach*

Almost all of the HAI models, deterministic or stochastic, adopted since the 1990s can be described as *state variable* models. State variables, such as population densities, number of susceptible individuals, and number of infectious individuals, are used to represent the states of the system as a whole. Typically, the analysis of the system is carried out by using a set of ordinary differential equations (ODEs). These models are also called 'population-level' models.

The mass-action principle: One of the key assumptions in these models is the *mass-action principle* [22]. It states that the number of new infections per time period (transmission rate) is proportional to the number of susceptible individuals times the number of existing infectious cases.

The transmission rate tr is given by the following expression:

$$tr = \beta \times S \times I \quad (1)$$

$$\beta = c \times tp \quad (2)$$

where S is the susceptible population density, I is the infectious population density, β is the transmission coefficient, c is the contact rate (average number of contacts per individual per day), and tp is the transmission probability per contact. In general, the values for these parameters are derived directly from observational data or by using a parameterisation procedure. Typical values reported in the literature are listed in Table 1.

The limitations of the mass-action hypothesis have been highlighted in several studies [15,17,18,23,24]. First, this principle implies that the population mixes homogeneously and that each susceptible and infectious individual is accessible to all others at all times. However, in general, the hospital population shows heterogeneity—patients may be grouped based on sex, age, clinical specialty, severity of illness, given treatments; spatial and/or personnel cohorting may be applied. Second, the movement of each individual staff member within a ward or an intensive care unit cannot generally be considered as random—e.g. the health-care workers may carry out ward rounds on a regular basis and in a set pattern. Third, the transmission rate, as defined by Eq. (1), is a state variable and, as a result, it does not explicitly include the role of individual behaviour in the transmission process. As a result, the individual properties, such as the status or the actions of each agent, cannot be properly represented in this kind of modelling approach.

Table 1 – Typical values for contact rate and transmission probability.

c = 1.38–7.60 [3,20,30,33]
tp = 0.01–0.15 [3,20,30–34]

2.2. *Exploring alternative approaches to HAI modelling. The individual-based approach*

The *individual-based* approach has been proposed as an alternative way of investigating infectious disease outbreaks in hospitals and small communities [7,8,25–27]. The individual-based approach is 'bottom-up': it starts at the bottom level of the system investigated, i.e. at the individual (agent) level, and it treats the individuals as unique and discrete entities. The individuals are allowed to interact and the dynamics of the system as a whole depends on these interactions. Thus, the study and the analysis of the system is carried out from the individual level upwards, towards the population level.

Some of the recent models adopting an individual-based paradigm are based on Network Theory [8,27]. When a scale-free network is used to represent the interactions among the (susceptible and infectious) agents, several nodes, called 'hubs', have an unusually high number of connections [28]. If a simulation can show that a given 'hub' individual has an higher probability of becoming infectious, control measures, such as isolation or treatment, could be applied in a selective way and, as a result, spread can be contained or reduced significantly.

There are several potential benefits in adopting an individual-based approach for the HAI problem. An individual-based model might: (a) help to better understand the impact of the population heterogeneities and the spatial distribution of the agents (locations, movement); (b) provide a detailed description of the temporal evolution of individual interactions (proximity events, contacts), actions (agent behaviours, policies and control measures applied, treatments provided), and events (admission, discharge, readmission of the patients).

On the other hand, this kind of modelling approach presents several limitations.

Since it implies a mechanistic understanding of the dynamics of the system under analysis, in general, a detailed description is required. Detailed and reliable observational data are required for comparison and, as a result, parameterisation and validation procedures can be difficult to implement. In some cases, its complexity might even make the model difficult to implement or computationally prohibitive (parallel computing might be the only option for handling the problem).

3. Implementation of the model

The modelling approach adopted here can be described as *individual-based* and *stochastic*. In order to study and analyze the spread of HAIs (MRSA infections) a computer simulation

has been developed [29]. The application is written in C++. The Direct Monte Carlo (DMC) method is applied to take the stochasticity of the system into account. The DMC method has an absolute estimation error that decreases with $N^{-1/2}$, where N is the number of simulation runs. The typical number of simulation runs performed is between 25 and 100. A discrete approximation (spatial and time discretization) is applied to the dynamics of the system. The temporal evolution of the system is taken into account by using two parameters: the *time step* and the *time scale*. The time step is set to 15 min. The time scale is the maximum time interval during which the system evolves. In this study, a time scale of 3 months is chosen.

In order to simulate the evolution of the system, the following factors are taken into account: the status and the movement of each agent, the contacts between individuals during a ward round, the hand hygiene compliance for each agent, and the control measures (spatial and personnel cohorting) applied.

The main parameters that characterize each agent (patient or caregiver) are: the *colonization status*, the *transmission probability*, and the *compliance factor*. For each patient, the user is required to specify the *admission day* and the *length of stay*. The dynamics of the health-care workers is treated in terms of the movement during a ward round. Generally, the activities carried out by the caregivers during the day are split up into shifts. The user can specify any kind of shifts by setting the parameters *shift start time* and *length of shift* explicitly in the input file.

The transmission dynamics of the infection is based only on the indirect transmission from patient to patient via health-care workers—at this stage, the model does not take into account the direct transmission from patient to patient or the indirect transmission from patient to patient via environmental surfaces. The caregivers may become transiently colonized in that they can carry MRSA on their hands if compliance with hand hygiene is poor. However, all caregivers are considered not colonized at the beginning of each shift.

The epidemic process strongly depends on the contact rate (Table 1 shows typical values for the contact rate reported in the literature). Within the simulation, the contact rate is almost equal to 1. This value follows from the current description of the agent dynamics within the model.

Since the main parameters associated with the transmission dynamics of the infection can be specified for each agent by the user, the simulation allows the study of MRSA outbreaks in the case of inhomogeneous distribution of transmission probability and/or compliance.

Simulation types: In the current version, the user can choose from two different types of simulation.

The aim of *Simulation Type 1* is to study the spread of an infection under well-defined conditions (populations, patient status, lengths of stay, assigned beds, caregiver status, shifts, etc.). In this case, a given system is analyzed during its evolution. No specific actions on the system (policies and control measures) are taken during the epidemic period.

The *Simulation Type 2* is for studies on space management. In this case, patient allocation procedures can be investigated. Control measures, such as spatial and personnel cohorting, can be applied to the system and, as a result, their effects evaluated.

In the case of a ward with four bays, under strict spatial cohorting, bay 1 and 2 are reserved for negative patients, and bay 3 and 4 are reserved for positive patients. All bed assignments during the time interval are made by the simulation according to given rules and constraints. The user is required to specify two parameters: the *maximum number of positive patients allowed in the ward each day* and the *cohorting factor*. The first parameter has an effect on the bed assignments, bed changes, and patient relocation to another ward or to single rooms. The latter controls the kind of personnel cohorting applied—e.g. according to the model conventions, if 20 caregivers are assigned to a ward each day and if a cohorting factor of 80% is applied, 8 caregivers are required to visit only the negative patients, 8 caregivers to visit only the positive patients, and the remaining 4 caregivers to visit all patients.

4. Settings and study design

The study was undertaken using routinely collected data on new cases of MRSA acquisition in a vascular ward with 4 bays, each containing 6 beds, at Ninewells Hospital (NHS Tayside).

Historical data for a period of 15 months (01.09.06-30.11.07) were processed and analyzed.

For the patients, the following information was collected: sex, age, admission/discharge/readmission day, and MRSA screening results. The patient population consisted of 859 women and 1022 men. The median length of stay was 4 days.

For the health-care workers, shifts details (start time and length) and hand hygiene compliance were collected. The average number of caregivers per day was 25. The patient care activities carried out by the staff during the day were divided into four shifts. No management strategy for specific personnel cohorting was applied. The average compliance with hand hygiene was 80%.

4.1. *Parameterisation*

The parameters describing the environment and the temporal evolution of the system were derived from the observational data; for a given time interval, all data associated with the admissions and discharges of the patients, the assigned beds, the bed changes, and the caregiver shifts were supplied to the simulation.

The values for the hand hygiene compliances in caregivers were estimated by using routine observational data. However, in the case of patients, no data were available and, as a result, the hand hygiene compliance values for this group were arbitrarily set at 50%.

The transmission probabilities (patient-to-caregiver and caregiver-to-patient) were set by using fitting procedures. In order to carry out the parameterisation, the observed prevalence data associated with a period of 4 weeks (03.03.07–01.04.07) were used as reference. The test values chosen for tp lay within a physically meaningful range based on data available from published studies (Table 1). In Table 2, the simulation results are compared with the observational data. The table shows the average number of positive patients per day, the average daily and monthly prevalence as function of the transmission probability.

Table 2 – Average number of positive patients per day, average daily prevalence, and monthly prevalence as function of the transmission probability. The observational data refer to the time interval between 03.03.07 and 01.04.07.

	Obs.	Simul.				
Transmission prob.	–	0.00	0.10	0.12	0.13	0.15
Pos. patients each day	8	1.85	5.19	6.77	7.97	10.13
Daily prevalence	0.381	0.086	0.246	0.322	0.379	0.481
Monthly prevalence	0.374	0.086	0.243	0.317	0.372	0.473

5. Results and discussion

Although the model is at an early stage of development, preliminary studies have already produced encouraging results. Primarily, the simulation has been able to reproduce prevalence patterns observed at Ninewells Hospital (Ward 11) during different time intervals.

The current version of the model was validated by using graphical methods, analysis of coefficients of determination, and analysis of incidence and prevalence.

The *Simulation Type 1* was used to study infection spread under well-defined conditions and to compare the model outputs with the data collected over an overall period of 22 weeks (01.02.07–02.03.07, 02.04.07–01.05.07, and 01.06.07–29.08.07).

Fig. 1 shows three curves referring to the time interval between 01.02.07 and 01.05.07; two curves (dotted and solid lines) are associated with the data collected in Ward 11, the third curve (dashed line) relates to the simulation results. The error bars associated with the last curve refer to the sample standard deviations (s)—note that the standard error of the mean (SEM) is related with s through the formula $\mathrm{SEM} = s/\sqrt{N}$, where N is the number of simulation runs. Two different scenarios were considered. In the first scenario (dotted line), the infection spread was not taken into account and, for each day, only the positive patients who were already positive on admission were counted. In the second scenario (solid line), on the other hand, the time series includes all the positive cases—the positive patients who were already positive on admission and those who were newly identified as positive during their stay in the ward.

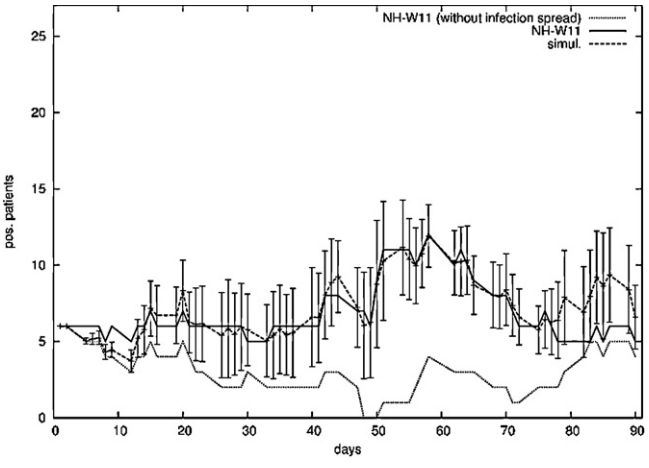

Fig. 1 – Number of positive patients as function of time (with or without spread of infection). The dotted and solid lines are associated with the data collected in Ward 11, Ninewells Hospital; the dashed line refers to the simulation results. The data refer to the time interval between 01.02.07 and 01.05.07.

By increasing the transmission probability tp, the simulation curve (dashed line) moves gradually from the first to the second scenario. For most of the time periods under investigation (14 weeks over 22), the best fit between simulation and observational data was achieved for $tp = 0.13$; for these cases, high values of coefficient of determination were obtained ($R_2 > 0.9$).

It is worth highlighting that some of the values used for the simulation parameters depend on the assumptions of the current version of the model. Future versions, that will include a better description of the agent dynamics and the indirect transmission from patient to patient via environmental surfaces, might require different values for these parameters.

5.1. *Combined effect of spatial and personnel cohorting*

The aim of cohorting is to minimise the possible interactions between individuals within a ward. This procedure has proved to be an effective infection control measure [1,13,14,30,31].

The *Simulation Type 2* was used to study the combined effect of spatial and personnel cohorting. In this study, 7 patients were eligible for admission every day (except the weekends) and, on average, based on the number of available beds, about half of them were actually allocated to the ward. It was assumed that, among the entire patient population who were eligible for first-time admission during a 3-month period, 5% had already had one admission to the ward. Patients were hospitalized for a period ranging from 1 to 34 days, with an average length of stay of 5 days. The admission prevalence of MRSA colonized patients was 10%. These assumptions are consistent with the observational data from Ninewells Hospital and with those reported in the literature [2,32].

First, a strict spatial cohorting (without personnel cohorting) was applied—all the positive patients were isolated in a confined space and each caregiver was required to visit all patients, positive and negative, during the shift. The maximum number of positive patients allowed in the ward each day was set to 12.

In this case, according to the simulation, a relatively high daily incidence (~4%) was recorded in the ward (for comparison, note that in the ward, where a partial spatial cohorting and no personnel cohorting are applied, the daily incidence was ~1% during the time interval 02.04.07–01.05.07).

This may be explained by the following considerations. 'Clustering' the positive patients increases the risk of colonization for the caregivers who look after them. As Fig. 2 shows, in the case of strict spatial cohorting with no personnel cohorting applied, a high number of health-care workers became colonized during the day. As a result, if during the shift the caregivers were required to visit both positive and negative patients, the infection would spread faster within the ward (see Fig. 3).

Then, a different scenario was analyzed. Both strict spatial cohorting and personnel cohorting were applied. In this case, the dynamics of the agents changed: some (or all) of the caregivers were 'cohorted' with a given group of patients and their

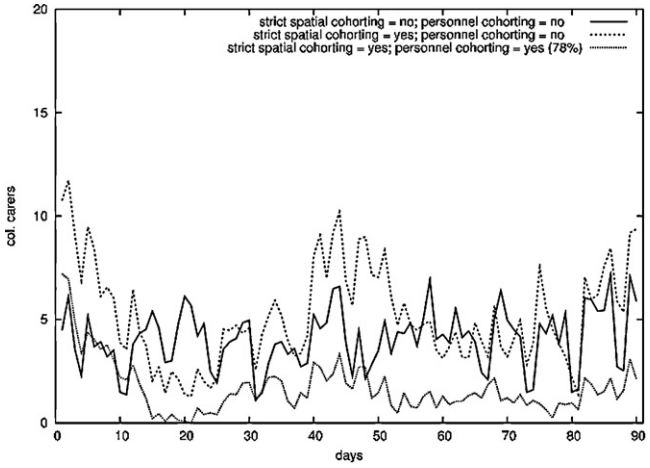

Fig. 2 – Number of colonized caregivers (transient carriers) as function of time for three different scenarios: [psc], [ssc], and [ssc + pc].

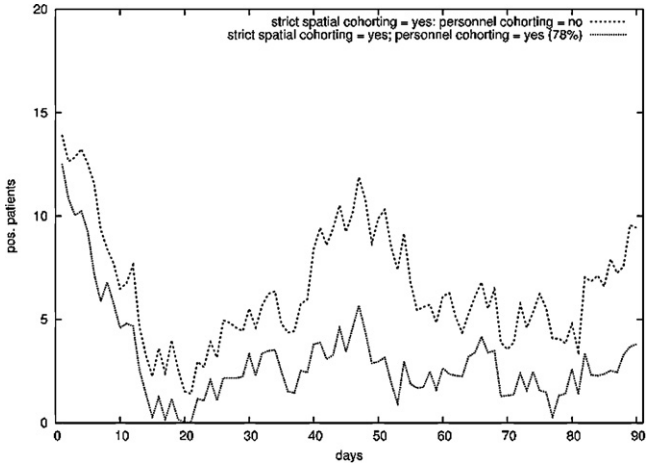

Fig. 3 – Number of positive patients as function of time for two different scenarios: [ssc] and [ssc + pc].

movement was confined in a restricted area of the ward. It followed that a lower number of health-care workers became colonized during the day (see Fig. 2).

Different degrees of personnel cohorting can be applied. However, a minimum value (77 ± 1%) was found that assured a low level of daily incidence (∼0.5%) and that, at the same time, excluded the necessity to relocate positive patients outside the ward—if the prevalence is high, it may be necessary to relocate positive patients to another ward or to single rooms several times during the 3-month period, because of the lack of beds available.

Table 3 shows the incidence and the prevalence associated with three different scenarios: [ssc] strict spatial cohorting without personnel cohorting (simulation data); [ssc + pc] strict spatial cohorting with personnel cohorting (simulation data); [psc] partial spatial cohorting without personnel cohorting (observational data from Ward 11, Ninewells Hospital).

Table 3 – Incidence and the prevalence associated with three different scenarios: [ssc], [ssc + pc], and [psc]. The observational data [psc] refer to the time interval between 02.04.07 and 01.05.07.

	ssc	ssc + pc	psc
Strict spatial cohorting	Yes	Yes	No
Personnel cohorting	No	Yes (∼80%)	No
Pos. patients relocated	Yes	No	–
Daily incidence	0.043	0.005	0.011
Daily prevalence	0.382	0.180	0.363

6. Conclusions

The model presented in this paper can be used to study the spread of nosocomial pathogens—such as MRSA or severe acute respiratory syndrome (SARS). The computer simulation allows to analyze the dynamics of the system associated with an HAI outbreak, to compare various scenarios and settings, and to investigate processes associated with different timescales. It also allows to carry out studies on space and personnel management and to test the effects of different intervention strategies, such as spatial and personnel cohorting.

The findings from this study suggest that a strict spatial cohorting might be deleterious, if it is not combined with a personnel cohorting.

Moreover, the analysis of the time series associated with the total number of positive patients in the ward has revealed a strong dependence of the prevalence on the distribution of the lengths of stay of the patients. There was good agreement between our model and observational data.

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