Application of Agent-based Simulation to the Modelling and Management of Hospital-acquired Infections

by

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Declaration of Authorship

I, Yang Meng, declare that this thesis entitled

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and the work present in it are my own. I confirm that:

- This work was done wholly or mainly while in candidature for this research degree;
- Where any part of this thesis has previously been submitted for a degrees or any other qualification at this University or any other institution, this has been clearly stated;
- Where I have consulted the published work of others, this is always clearly attributed;
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself; and
- During the preparation of this thesis, several papers were presented and published as listed below. The remaining parts of the thesis have not yet been published.

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Abstract

Hospital-acquired infections (HAIs) are a big threat to the well-being of patients and place a heavy burden on hospital resources. The thesis provides the first attempt to apply agent-based simulation (ABS) to describe the transmission dynamics and evaluate the intervention policies of HAIs in general and Methicillin-resistant *Staphylococcus aureus* (MRSA) in particular.

Based on the proposed taxonomy of potential methods for modelling HAIs, the relative advantages of ABS compared to other modelling methods are investigated. The comparison provides a theoretical justification to the use of ABS. The main methodological issues, including the representation of patient agents and the modelling of the transmission process, are discussed and a framework of applying ABS on HAI modelling is proposed.

Guided by the framework, a MRSA model is built and validated using observed data from an empirical study. The model is more realistic and flexible than previous MRSA models and embeds intervention policies that have not been systematically studied such as the turnaround time and frequency of screening tests and the decolonisation treatment. Various interventions and influencing factors are systematically evaluated by formal experimental design methods including the fractional factorial design and the response surface design.

The experimental results indicate that the use of rapid screening tests with shorter test turnaround time is the most effective policy to reduce MRSA transmission in the hospital setting. The introduction of admission and repeat screening is another effective policy; however, the effectiveness is not linear and may depend on patients' lengths of stay. Providing more isolation facilities is also an effective policy but its effectiveness is significantly dependent on the efficacy of isolation.

To demonstrate the potential and flexibility of ABS, the MRSA model is extended to include a competitive infection, to include multiple hospital units and HCW agents, and the wider community.

Abbreviations

ABS	Agent-based Simulation
DES	Discrete-event Simulation
HAI	Hospital-acquired Infection
HCW	Healthcare Worker
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
MRSA	Methicillin-resistant *Staphylococcus aureus*
NHS	National Health Services
PCR	Polymerase Chain Reaction
SD	System Dynamics
S&D	Search-and-Destroy
VRE	Vancomycin resistant enterococci

Definitions

Length of Stay	The duration of time when a patient stays in the hospital.
Nosocomial Infection	An infection which is acquired when a patient stays in the hospital.
Primary Case	Patients who have already been colonised with a certain type of hospital-acquired infection when admitted to the hospital.
Relative Risk	The risk of acquiring an infectious disease in a group of people who are exposed to a risk factor, relative to a group who are not exposed to it.
Secondary Case	Patients who do not have a certain type of hospital-acquired infection when admitted, but who acquire the infection during the hospital stay.
Sensitivity	The proportion of actual positives which are correctly identified by a screening test.
Specificity	The proportion of negatives which are correctly identified by a screening test.

Chapter 1

Introduction

1.1 Introduction

The main theme of the thesis is to apply agent-based simulation (ABS) to model the transmission dynamics of hospital-acquired infections (HAIs) and to use the model to evaluate a range of intervention policies aiming at preventing and controlling the HAI of interest. ABS is a type of modelling and simulation technique which has been applied to many domains. HAIs, on the other hand, are a major threat to patients in the hospital and have been extensively investigated by clinical and, in recent years, by modelling studies. The main task of the thesis is to link the two topics and make a contribution both to extend the application area of ABS and to develop the understanding of HAIs so that the infectious diseases can be better managed in the hospital setting.

This chapter sets the background for this thesis. It describes the threat and distinctive features of HAIs. The potential intervention policies to prevent and control HAIs, and the problem areas facing HAI management are summarised. Then, ABS is introduced regarding its definition, features and applications to infectious diseases. Finally, the Birmingham Heartlands Hospital case study is introduced based on which the ABS model in the thesis is built and validated against. This chapter forms the basis on which later chapters will build.

1.2 Hospital-acquired Infections

1.2.1 Threat of Hospital-acquired Infections

Infectious Diseases

Infectious diseases have been a threat to people's survival, health and well-being since human life began (Department of Health 2002). In one of the most notorious epidemics in human history, around 25 million people died, out of a population of roughly 100 million, from bubonic plague in Europe in the fourteenth century. In the UK, more than 68,000 people died during the 1665 plague epidemic in London. Even in the early twentieth century, it was estimated that Russia suffered about two and a half million deaths from typhus between 1918 and 1921; and 20 million people were estimated to have died during the world epidemic of influenza in 1919.

Currently, many infectious diseases, such as smallpox, are almost eradicated or successfully contained in the developed world and increasingly in the developing world. The main reasons for the success may be attributed to the scientific advancement, most importantly the development of vaccine against many infectious diseases and the successful vaccination programme for a large proportion of human population, especially new-born babies. Another important reason for the success is the improved living standard of most parts of the worlds as reflected by higher standards of hygiene, access to clean water and better nutrition (McNeill 1976; McKeown 1979).

Despite of the significant advances in the human's battle against infectious diseases, there is still and will always be a threat from the infectious diseases for the well-being of the human race. Emerged in the twentieth century, the human immunodeficiency virus (HIV) has become a big healthcare, as well as economical and political problem for the developed and developing world alike. Worldwide, nearly 25 million people died from HIV from 1982 to 2007 and the number of people living with HIV in 2007 is 33.2 million, among which 2.5 million are children (World Health Organization 2007). The situation in developing countries, especially African, are worse than developed countries (Morgan and Whitworth 2001). Apart from HIV, many infectious

diseases, such as tuberculosis and malarias, are still posing a tangible risk to millions of people in the developing world where the living standard is low and mass vaccination programme can not be effectively delivered. According to the Department of Health (2002) in the UK, infectious diseases account for 41% of the global disease burden with infections such as HIV, tuberculosis and malaria accounting for millions of deaths in the world's population each year; and in England which is one of the wealthy industrialised countries, 40% of people consult their doctors every year because of an infection and infections account for 70,000 deaths each year.

Hospital-acquired Infections

HAIs, or nosocomial infections, can be defined as infections acquired in a hospital by a patient who was admitted for a reason other than that infection (World Health Organization 2002). HAIs made resurgence during the last three decades of the 20th century and are now a major problem for the National Health Service (NHS) in the UK (Department of Health 2002) as well as around the world. Healthcare associated infection is an even wider term which includes infections acquired not only in hospitals, but also in the primary care, community clinics, nursing homes and other healthcare facilities. In this thesis, the research is focused on HAIs that can be transmitted among patients in the hospital setting either through direct patient-to-patient contacts or by cross transmissions which are facilitated by healthcare workers (HCWs) or other human (e.g., visitors) or non-human (e.g., medical equipment) vectors. Transmissible HAIs are caused by contagious or communicable pathogens, and in most cases the pathogens are in the form of bacteria or viruses.

Impact of hospital-acquired infections

HAIs can severely detriment patient welfare and place heavy burdens on healthcare resources (Plowman *et al.* 1999). HAIs add to functional disability and emotional stress of the patient and may, in some cases, lead to disabling conditions that reduce the quality of life. HAIs are also one of the leading causes of death. Each year in the UK, around 5,000 deaths might be primarily attributable to HAIs and in a further 15,000 cases HAIs might be a substantial contributor (Department of Health 2002). A prevalence survey conducted under the auspices of World Health Organization in 55 hospitals of 14 countries showed an average of 8.7% of hospital patients had HAIs; and at any time, over 1.4 million people worldwide suffer from infection

complications acquired in a hospital (World Health Organization 2002). In the UK, about 9 percent of patients in the hospital have a HAI, making an estimated total of 100,000 patients a year; and the cost of increased length of stay and treatment is thought to be about £1,000 million a year (Noah 2006). Increased length of stay accounts for most of the extra financial cost, with the average increase for surgical wound infections to be 8.2 days (Coello *et al.* 1993).

Types of hospital-acquired infections

Currently, the widely known and studied HAIs in the UK and around the developed world include Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* (*C. difficile*). *Staphylococcus aureus* is normally susceptible to methicillin and several other antibiotics. It is a common cause of skin, wound and most seriously blood stream infection. MRSA which is first documented in 1960s, on the other hand, is resistant to methicillin and also to many other anti-staphylococcal antibiotics that makes it very difficult to treat. In 1997, the first strain of MRSA resistant to vancomycin, the drug usually kept in reserve for treating highly resistant strains, was reported in Japan (Hiramatsu *et al.* 1997). MRSA has become endemic in the UK, the USA, some other European countries, and elsewhere. MRSA as a proportion of all *Staphylococcus aureus* causing blood stream infections has risen from abut 2% in 1990 to more than 40% in 2000 (Johnson *et al.* 2005).

It was estimated that MRSA infections, on average, may increase patient's length of stay by two days and incur an extra cost of £6,916 per infection in a UK hospital (Cosgrove et al. 2005). MRSA is important also because staphylococci are virulent and they are associated with high fatality rate. In England and Wales, the number of deaths involving MRSA increased from 51 in 1993 to 800 in 2002; and the mortality data was matched by an increase in laboratory reports of MRSA bacteraemia, increasing from 210 reports in 1993 to 5,309 reports in 2002 (Griffiths *et al.* 2004)

C. difficile is the leading cause of nosocomial infectious diarrhoea in adults and it is responsible for large outbreaks (Cartmill *et al.* 1992). It can be transmitted by hands of HCWs, other patients, medical equipment and simply the background environment. In most cases *C. difficile* infection is asymptomatic, and overt infection may be

triggered by antibiotics and the presence of risk factors such as age, anti-diarrhoeal drugs and insertion of tubes/enemas into the gastrointestinal tract (Noah 2006).

Apart from the type of pathogen that causes the infection, HAIs can also be classified based on the clinical body sites of the infection. The main body sites that are susceptible to HAIs include blood, urinary tract, respiratory tract, surgical site and gastrointestinal tract. Blood stream infections account only for about 5 percent of HAIs but have a high mortality rate, and are mostly associated with an intravascular device and the admission to intensive care units (ICUs) (Noah 2006). Urinary tract infections are the most common type of HAIs and are also commonly associated with indwelling catheters. Pneumonia is the second most common HAI and it has a high fatality rate; and patients who are intubated or on ventilators are at a higher risk. Surgical site infections include wound infections or deep cut infections; and both patient and surgical factors may affect surgical site infections. Although almost all gastrointestinal organisms transmissible among people may cause HAI, the most common pathogens are *C. difficile*, rotavirus, norovirus and salmonella.

1.2.2 Key Features of Hospital-acquired Infections

Compared to non-HAIs (i.e., community-acquired infections), HAIs have some distinctive characteristics. Because of these special features, the clinical study methods, the prevention and control policies, and the analytical and modelling methods which are designed for community-acquired infections (e.g., HIV, malaria and various sexual-transmitted infections) may not be appropriate to be directly applied to infections in the hospital setting.

Rapid Patient Turnover

One of the distinctive features of HAIs compared to community-acquired infections is the rapid turnover of patients in the hospital. The actually length of stay may vary for patient with different diseases and risk factors; however, patients normally only stay in a hospital for a couple of days, or few weeks at most (Austin and Anderson 1999; Cooper and Lipsitch 2004). For example, the average length of stay in the UK is about 6.8 days in year 1999-2000 (Black and Pearson 2002).

The rapid turnover of patients has many implications for the transmission dynamics in the hospital. On one hand, the positive effect is that, even without specific intervention policies, colonised or infectious patients who have the ability to transmit the pathogen may leave the hospital system in a few days (i.e., discharged) and no longer pose a threat to other susceptible patients in the hospital. On the other hand, even with every possible and effective intervention policy, new cases of infection may still be constantly introduced to the hospital by admitting patients from the community who have already been colonised with the pathogen. The rapid turnover of patients also indicates that some intervention polices to combat HAIs must be prompt relative to the patients' lengths of stay; otherwise, patients may be discharged before the intervention policy takes effect. For example, screening tests for identifying MRSA colonised patients which take seven days to obtain the results may have limited value to patients who stay in the hospital for less than a week (which may include most of the patients in the hospital).

Small Patient Population

Another special feature of HAIs is the small patient population in the hospital setting. When studying community-acquired infections, the population size is normally in the order of tens of thousands of people for a town, millions for a city, or tens of millions or even billions for large-scale national or international studies. For HAIs, the patient population size is much smaller. A big hospital may at most have few thousand in-patients at the same time. For many studies which focus on a single hospital unit, the patient population normally ranges from less than 10 for an ICU to about 40 for a big surgical or medical ward.

It is common to observe big fluctuations of infection prevalence (i.e., the proportion or the number of people with the infectious diseases) in a small patient population and stochastic chance effects may dominant the transmission dynamics within a small population (Austin and Anderson 1999; Cooper *et al.* 1999; Pelupessy *et al.* 2002).

Due to the randomness and chance effects, an outbreak of HAI may happen and prevalence may be high even when effective interventions are implemented. On the other hand, even with ineffective interventions or no interventions at all, there may be a chance that an outbreak does not happen and the prevalence is low for a certain

period of time. Therefore, conclusions drawn from a single observation or even a couple of observations within a shorter period of time may not represent the true nature of the transmission dynamics of the HAI of interest. The modelling methods to study HAIs should be able to handle stochastic systems, either analytically or through simulation replications.

Asymptomatic Carrier

Many HAIs, such as MRSA and *C. difficile*, may stay in a healthy people for a long time without causing any clinical recognisable symptoms, but still have the ability to transmit to other susceptible patients (Austin and Anderson 1999; Cooper and Lipsitch 2004; Smith *et al.* 2004). Due to asymptomatic carriers, unless pre-emptive screening tests are carried out in the hospital, it is very difficult to identify and consequently prevent these patients from transmitting the pathogen to other susceptible patients. The existence of asymptomatic carriers and the lack of pre-emptive screening strategy in most hospitals imply that detailed transmission dynamics of HAIs are normally a hidden process and are difficult to observe.

In epidemiology, asymptomatic carriers are normally known as colonised patient while clinical symptomatic carriers are known as infected patients. Colonisation is important since it may be transmitted to other patients and can lead to infections which may have serious consequences. Since the focus of the research is to study the transmission of HAIs, the term 'colonised patients' are used hereafter in the thesis to refer to both colonised and infected patients who have the capability of transmitting the pathogen to susceptible patients.

Endemicity in the Hospital

Some HAIs, such as MRSA and *C. difficile,* are endemic in hospitals in many counties because of the large reservoir built up in the community. Once a significant proportion of people in the community are colonised with a certain type of HAI, asymptomatic carriers may bring the pathogen to the hospital and become a constant source of threat to susceptible patients in the hospital through new hospital admissions.

For counties where certain types of HAIs are endemic, it is unrealistic in the short-term to totally eradicate the pathogens in the hospital setting. Alternatively, the focus

of intervention policies should be how to prevent new secondary transmission cases (i.e., patients who do not have a certain HAI on admission, who acquire the infection during their stay in the hospital), and how to identify and treat primary case patients (i.e., patients who have already been colonised with a certain HAI on admission). In the long term, these interventions should gradually reduce the community reservoir of asymptomatic carriers and eventually eradicate the HAI from the community and the hospital.

1.2.3 Intervention Policies for Hospital-acquired Infections

There are many intervention policies that have been implemented or are proposed to control and prevent HAIs. One popular strategy which has been proved effective both in theory (Bootsma *et al*. 2006) and in practice (Cooper *et al.* 2004) to combat HAIs such as MRSA is the "Search-and-Destroy" (S&D) strategy. The fundamental idea of the strategy is to pre-emptively "search" patients who are colonised with a pathogen through screening tests followed by measures to "destroy" (e.g., isolation and decolonisation treatment) the pathogen so that these identified patients can not transmit the pathogen to other susceptible patients. The S&D strategy may include the following detailed policies:

- "Search" policies:
    - Screen all or high-risk patients on admission; and
    - Screen all or high-risk patients repeatedly during their hospital stay.
- "Destroy" polices:
    - Isolate identified colonised patients;
    - Pre-emptively isolate high-risk patients on admission;
    - Decolonise identified colonised patients; and
    - Apply barrier precaution measures (e.g., the use of single-used gloves) for identified colonised patients.

Apart from the aggressive and dedicated S&D strategy, there are many general policies which are recommended to be carried out in hospitals to prevent and control HAIs. These general measures may include:

- Hand-washing by HCWs before and after contacts with patients;
- Standard contact precautions with patients;

- Disinfect medical equipment, especially invasive medical devices;
- Use invasive medical devices only when necessary and keep the devices in for as short as possible;
- Ward cleaning and decontamination;
- Antibiotic prescription policy (i.e., restrict the use of antibiotics);
- Education of healthcare staff; and
- Ward closure.

In the UK, the healthcare authority (i.e., the Department of Health) has outlined in the *Health Act* not only general measures to prevent and control HAIs, but also specific policies aiming at MRSA and *C. difficile* (Department of Health 2006). To control and prevent MRSA, following policies must be carried out in NHS hospitals in the UK: (1) admission screening for all elective patients (by March 2009); (2) provide screening to emergency patients as soon as is practical, (3) decolonisation treatment for identified colonised patients; (4) isolation for identified infected or colonised patients; (5) transfer infected or colonised patients within NHS hospitals or to other healthcare facilities; and (6) antibiotic prophylaxis for patients who undergo surgery. For *C. difficile*, the code specifies the following policies: (1) active surveillance; (2) isolation for infected patients or cohort nursing; (3) environmental decontamination; and (4) antibiotic prescribing policies.

1.2.4 Problem Areas for the Management of Hospital-acquired Infections

Due to the distinctive features of HAIs, namely the rapid turnover of patients, the small patient population, asymptomatic carriers and the endemicity in hospitals, and numerous dedicated or general intervention policies, the management of HAIs is a complex and challenging issue. The special characteristics of HAIs mean that the findings and recommendations to deal with community-acquired infections, which have been the main areas of epidemiological study in the past, may not be directly applied to HAIs. The abundant choices of intervention policies further complicate the management of HAIs because the effects of different policies may be entangled with each other which make it difficult to evaluate the effectiveness of a single policy and to determine the interactions among different policies. Consequently, taking into

account of chance effects and randomness, some of the main problem areas of the management of HAI include:

- How to evaluate the effectiveness of a single intervention policy to prevent and control HAIs without confounding with other policies which may be implemented at the same time;
- How to evaluate the interactions among different intervention policies, and how to determine the most effective intervention strategy which involves a number of intervention policies;
- How to quantify the impact and sensitivity of the uncontrollable influencing factors that may have a big impact on the transmission dynamics of HAIs; and
- How robust is each single intervention policy and is each feasible intervention strategy, taking into consideration of the influencing factors.

1.3 Agent-based Simulation

1.3.1 Definitions of Agent-based Simulation

Partly as a result of the different names such as agent-based modelling, bottom-up modelling, multi-agent systems and individual-based modelling, there is no universally agreed definition for ABS. Wooldridge (200) defined multi-agent systems as systems composed of multiple interacting computing elements, known as agents. Sanchez and Lucas (2002) defined ABS as a simulation made up of agents, objects or entities that behave autonomously, and these agents are aware of and interact with their local environment through simple internal rules for decision-making, movement and action. Macal and North (2006) deemed ABS as a new approach to model systems comprised of interacting autonomous agents. There is no attempt to propose a new definition for ABS in this thesis; instead, a loose definition is given which satisfies most previous definitions. In this thesis, ABS is defined as a computer simulation made up of multiple autonomous agents who can interact with each other and with the system environment according to their behaviour rules.

1.3.2 Features of Agent-based Simulation

ABS is founded on the notion that the whole of many systems is greater than the simple sum of its constituent parts, and the systems must be understood as collections of interacting components, each of which has its own rules (North and Macal 2007). Consequently, the aggregate behaviour of the simulated system is the result of the dense interactions of relatively simple behaviours of the individual simulated agents (Sanchez and Lucas 2002). Compared to traditional modelling approaches, such as mathematical modelling, SD and DES, the key features of ABS is a bottom-up, rather than top-down, modelling approach and the focus is on defining the attributes, states and behaviour rules of individual agents.

Compared to the traditional top-down modelling approach from the perspective of the overall system, the bottom-up modelling approach adopted by ABS has the following characteristics:

- Regarding model developments, the building of the model normally starts from defining the attributes, states and behaviour rules (e.g., how the agent changes state, how agents interact with each other, and how the agent interacts with the environment) of different types of agents;
- Regarding model dynamics, the model is driven by the dynamics of each individual agent and the interactions among them, and system behaviour naturally emerges from the collective behaviours of locally defined agents; and
- Regarding model contents, the representation of the attributes, states and behaviour rules of agents constitutes the main part of the model, and requires most of the efforts and time to develop the model.

1.3.3 Type of Agents

Agent is the core and most important element for ABS. There is a general consensus that the agent needs to be autonomous but there is little agreement beyond this because the potential properties vary in their importance in different domains (Wooldridge 2002). Bonabeau (2001) considered any type of independent component to be an agent, allowing an agent's behaviour to range from primitive reactive decision rules to complex adaptive intelligence. Jennings (2000), from the perspective

of computer science, suggested that the only fundamental feature of an agent is the capability to make active independent decisions. Casti (1997) argued that agents should not only contain base-level behaviour rules but also should be subject to rules which can change over time due to experience and memory (i.e., be adaptive). Mellouli *et al*. (2003) also recommended that a component's behaviour must be adaptive in order for it to be considered as an agent.

Macal and North (2006) defined an agent as potentially having the following five properties: (1) an agent is an identifiable and self-contained discrete individual with a set of rules governing its behaviours and some decision-making capability; (2) it is situated in an environment within which it interacts with other agents as well as the environment; (3) it may be goal-directed which means it can compare the outcome with its goals; (4) it is autonomous and can function independently in the environment; and (5) it may have memory and learn and adapt its behaviours based on experience. They also argued that agents may have some but not all of these properties and, in order to be deemed as an agent, the model should be structured in such a way that missing features can be easily added within the established modelling framework (North and Macal 2007). Drogoul *et al.* (2003) also argued that many agents in real-world ABS applications only use a weak notion of agent and do not have goals or memories, and can not adapt based on experience.

In this thesis, the concept of agent fits in with Macal and North. In the context of HAI modelling, patients and potentially HCWs are the most important types of agents. The basic requirements of patient or HCW agents are that they need to be self-contained independent individuals who are situated in the hospital environment and may interact with other agents and the hospital environment. Apart from the basic requirements, the patient or HCW agents may or may not have more advanced features such as goal-directed, having memory and being adaptive. Therefore, depending on the assumptions of the model, patient or HCW agents may range from simple reactive agents to sophisticated intelligent agents.

1.3.4 Applications of Agent-based Simulation to Infectious Diseases

In epidemiology modelling, most existing individual-based models focused on community-acquired infections such as HIV, influenza and various types of sexual-

transmitted diseases. There are only a few individual-based models that studied the transmission of HAIs (see Section 2.3). People or patients in these models are represented as identifiable and self-contained discrete individuals who have some states and who can change their states according to some rules. They may be labelled as ABS according to the definitions of ABS and agents adopted by this thesis (see Section 1.3.3). However, it is not until recently that some of these models used the term "agent-based simulation" or "agent-based modelling". Some of the early individual-based models labelled themselves as "micro-population model/simulation" or "discrete individual model".

Ackerman *et al.* (1990) proposed a micro-population model to simulate the epidemics of influenza. In the model, the disease progression of each person was updated on an individual basis and complicated assumptions regarding mixing, disease progression and individual heterogeneity were made. A stochastic model to study the dynamics of HIV in central African cities was built by Auvert *et al*. (1990). Each individual in the city population was separately represented. The birth and death, sexual behaviour, injections and transfusions and HIV development were discretely evolved by examining each individual at each successive step. The model also applied a flexible Monte-Carlo method. Ghani *et al.* (1997) applied a stochastic individual-based model to study the role of sexual partnership networks in the transmission dynamics of gonorrhoea. An individual-based micro-population model was proposed by Van Der Ploeg *et al*. (1998) to study the transmission, consequences and intervention policies of HIV and sexually-transmitted infections. The model was applied to an empirical study in Nairobi, Kenya.

Some individual-based simulators were proposed to study the transmission of community-acquired infections in general. Peterson *et al*. (1993) proposed VESPERS (Viral Epidemic Simulation Programs for Epidemiological Research Studies), a stochastic micro-population simulation platform for the modelling of community-acquired infections. Individuals in VESPERS can move through various states and may have individual demographics, susceptibility and infectivity. The platform also supports mixing groups. Adams *et al.* (1998) proposed HIVSIM, an individual-based modelling environment developed in C++ and based on previous micro-population simulation platforms, to evaluate HIV vaccine trial designs. Another simulator,

GERMS (Geographic-Environmental Re-infection Modelling Simulator), was proposed by Adams *et al.* (1999) to model the transmission of sexually-transmitted infections. The simulator has the ability to represent heterogeneous individuals with different social and geographic characteristics, interactions among individuals, transmission probabilities, infection duration, and contact and infection histories.

More recent studies began to label the individual-based models as ABS or agent-based model. Bagni *et al.* (2002) proposed an ABS model to study the spread of Bovine Leukemia, a pathogen which exclusively infects cattle in dairy farms. The model was built in both the Swarm environment (a collection of libraries written in C language to build ABS models) and Java. The model was event-driven and has the capability of event-scheduling. In the proposed model, it is possible to trace the evolution of the clinical states of each animal (e.g. healthy or infected). Spatial movements of the animals may also be represented.

A general agent-based spatially explicit epidemiological model was proposed by Dunham (2005). The model structure is embedded within social networks. Classic epidemic models, such as SIS (susceptible-infected-susceptible) and SIR (susceptible-infected-removed), were implemented and tested under this framework. The framework is suitable for community-acquired epidemics with large numbers of agents. The model was built in the MASON toolkit which is a set of non-commercially available Java-based ABS libraries.

A large-scale and distributed ABS model was developed by Parker (2007) which is capable of simulating hundreds of millions of agents and can be distributed to several compute nodes to share the burden of enormous computing requirements. The study focused on solving computational and technical problems of dealing large number of agents in connected compute nodes. Bobashev *et al.* (2007) proposed a hybrid agent-based and equation-based modelling approach in order to combine the advantages of both modelling paradigms. The study recognised that ABS model is powerful in describing epidemiological processes involving human behaviours and local interactions. The fundamental idea of the hybrid approach is to apply ABS model at the start of the epidemic and switch to equation-based model after the number of

infected individuals is large enough to support population-averaged equation-based approach.

1.3.5 Other Applications of Agent-based Simulation

ABS has been widely applied to different domains which include financial market (LeBaron 2002), supply chain management (Nilsson and Darley 2006; Albino *et al.* 2007), human resource allocation (Marin *et al.* 2006), retail management (Siebers *et al*. 2007), electricity market (Bunn and Oliveira 2007), digital market (Lopez-Sanchez *et al*. 2005), social science (Gilbert and Terna 2000), general economics (Sprigg and Ehlen 2007) and general management research (Robertson 2005).

1.4 Empirical Case Study

The building of a simulation model was originally part of a research study (Hardy *et al.* 2007), funded by the Department of Health in the UK, to test whether screening MRSA using a rapid Polymerase Chain Reaction (PCR) test, which may provide results within a day, is more effective and cost-effective than the established culture test which may take up to four days to obtain the results. The main research study was carried out at Birmingham Heartlands Hospital, a typical large general teaching hospital in the UK which has more than 1,000 beds. The project involved seven surgical wards and lasted for sixteen months. Detailed description of the research project is discussed in Section 4.2.1. The research study provides the background to build the ABS model of MRSA in the thesis. The proposed MRSA model is also configured with and validated against observed data from the empirical study.

Chapter 2

Modelling Hospital-acquired Infections

2.1 Introduction

Modelling is a valuable tool to study the transmission dynamics of infectious diseases. There have been plenty of previous studies applying various techniques to model the transmission of HAIs. A systematic review of the literature will identify potential gaps in existing research and justify the contributions of the thesis.

2.2 An Introduction to Infectious Disease Modelling

2.2.1 Developments of Infectious Disease Modelling

There is a long history of applying mathematical models to study the spread of infectious diseases. The first work can be dated back to the eighteenth century (Bernoulli 1760) who used a mathematical method to evaluate the effectiveness of the variolation techniques against smallpox. However, it was not until the early nineteenth century that dynamical system approaches were applied to epidemiology. Since then, the application of mathematical models to study epidemiology has witnessed numerous significant conceptual and technical developments in the early twentieth century. For example, Brownlee (1906) fitted Pearsonian frequency distribution curves to a large series of epidemics. Hammer (1906) suggested that the course of an epidemic depends on the rate of contact between susceptible and infectious individuals which later became one of the most important concepts in epidemiology modelling: the “mass action” assumption in which the net rate of spread of infection is assumed to be proportional to the product of the density of susceptible individuals times the density of infectious people. In another milestone work, Kermack and McKendrick (1927) established the well-known threshold theory according to which the introduction of a few infectious people into a community of susceptible people

will not incur an epidemic outbreak unless the density or the number of susceptible people is above a critical value. Hamer (1906), Ross (1911) and Moshkovskii (1950) applied quantitative methods to study the regular recurrence of measles epidemics and the relationships between numbers of mosquitoes and the incidence of malaria. According to Anderson and May (1992), they were the first to formulate specific theories about the transmission of infectious diseases in simple but precise mathematical statements, and along with other studies (Ross and Hudson 1917; Kermack and McKendrick 1927; Soper 1929) they provided a firm theoretical framework for the investigation of observed patterns of infectious diseases.

Since the early beginnings, there was a steady growth in the literature concerning epidemiology modelling. More research areas were explored including the stochastic treatment of the models, the spatial spread of diseases, the importance of heterogeneity in the transmission, and the study of intervention policies. A full review of the recent development of modelling community-based infections is out of scope of the thesis. For a comprehensive review of the development of infectious disease modelling, please refer to texts by Bailey (1975), Anderson and May (1992), Grenfell and Dobson (1995), Daley and Gani (1999) and Hethcote (2000).

2.2.2 Values of Modelling as a Decision Supporting Tool

There are many reasons why modelling can be a useful tool to support the decision making of preventing and controlling infectious diseases. These values can be applied not only to infectious disease modelling in general, but also to the modelling of HAIs. The values of modelling these systems include the following aspects:

Real experiments are not practical

One main reason why models are built to study biological systems is that real experiments to study infectious diseases can be time-consuming, costly and even unethical to carry out (Peck 2004). This is particular true for the studies of rare infections and those studies that focus on the evaluation of intervention policies such as vaccine programme, screening programme and isolation. Modelling, under such circumstances, can be the economical or even the only option to conduct the research.

Disclosing the transmission dynamics

One of the basic functions of the infectious disease models is to disclose the transmission dynamics of the disease under study (Koopman 2004). For example, an influenza model can reveal the number of people in a city who will catch the virus during the winter; a MRSA model can describe the changing numbers of colonised patients and the occupancy of the isolation rooms in the hospital through time. The transmission dynamics can be presented mathematically by analytical solutions or, increasingly, by diagrams based on numerical simulations. Some advanced simulation techniques, such as visual interactive interface and virtual reality, may help to communicate the transmission dynamics more effectively to the audience.

Quantitative predictions and quantify the effectiveness of intervention policies

Models can normally provide quantitative predictions about the spread of the infectious diseases such as the number of susceptible and colonised patients through time. If models have enough detail and are properly verified and validated, they can provide reasonably reliable predictions. The effectiveness of various interventions can also be quantified through systematic model experimentations, if the intervention polices can be embedded into the model and the observed data are available. Bonten *et al.* (2001) suggested that the use of a theoretical framework to conceptualise the underlying process of infection transmission and its subsequent modelling formulation may help the quantification of the transmission process and the effectiveness of infection control measures.

Focus on key factors and relationships

The modelling practice itself will force the researchers to focus on the most important factors and relationships that affect and define the transmission dynamics, and to ignore the less important ones. As Cooper (2007) argued that mathematical infection models simplify the system being studied to only the most essential characteristics and as a result can yield the most profound insights about the factors determining a system's behaviour.

2.3 Previous Hospital-acquired Infection Models

Although the modelling study of infectious disease has a long history, these early studies generally focused on community-based infections rather than HAIs. The theory developed based on community-based infections may not be directly applied to HAIs due to the distinctive natures of HAIs such as the rapid turnover of patients, the small patient population, the asymptomatic carriers and the endemicity in the hospital (see detailed discussion in Section 1.2.2). This section reviews the previous studies on HAI modelling.

2.3.1 First Attempts

Mathematical Compartmental Models

The first modelling study on HAIs appears to be carried out by Massad *et al.* (1993) who investigated the evolution of antibiotic resistance in the hospital setting based on the classical SIR (susceptible-infected-removed) model which was previously used to study community-based infections. The model only considered the patient population which was divided into three compartments: susceptible, infected by antibiotic sensitive strain and infected by antibiotic resistant strain. A system of three ordinary differential equations, which describes the dynamics of the number of patients in each compartment, was evaluated deterministically by both analytical and numerical methods. Equilibrium analysis was performed to study which strain of the pathogen would dominate, and observed data from other studies were used to configure and validate the model. The authors admitted that the model is a very crude description of the real world and the weakest point of the model is the assumption of homogeneous mixing of patients and the resultant mass action assumption on the infection transmission.

Sebille *et al.* (1997) described the outbreak of a nosocomial pathogen in a hospital ICU using a mathematical compartmental model. Not only patients, but also HCWs as intermediate human vectors (HCWs get transiently or permanently colonised from a patient and pass the pathogen to other patients) were explicitly represented in the model. Both patients and HCWs were divided into three compartments: uncolonised, colonised with sensitive strain and colonised with resistant strain. Two transmission

routes were explicitly modelled: patient-to-patient direct transmission and cross transmission between patients through HCWs. Compared to the previous study, although the model was also treated deterministically, the objectives of the model included the evaluation of some intervention policies such as hand-washing compliance among HCWs, antimicrobial policy and reducing the admissions of patients who are already colonised with the pathogen. The study suggested that modelling appears to be a valuable tool for the evaluation of the effectiveness of various intervention policies.

Austin and Anderson (1999) proposed a series of mathematical models to study the emergence and spread of antibiotic resistance pathogens, such as MRSA and vancomycin resistant enterococci (VRE), on scales ranging from within the patient, in hospitals and within communities. The hospital-level model consisted of both patients and HCWs who were classified as either colonised or uncolonised. Transmission dynamics were also described by a system of four ordinary differential equations, each representing the change in the number of paitents/HCWs in one compartment. Notably, the model was not only treated deterministically, but also stochastically by both analytical method and numerical realization. The model was applied to the spread of VRE in an ICU, and the main objective of the model was to assess the relative merits of different intervention policies including hand-washing compliance, HCW-patient ratio, and single and multiple drug therapies for decolonisation. The model was not configured with observed data.

In a separate paper of the same year, Austin *et al.* (1999) described in detail the application of a mathematical compartmental model on VRE in a hospital ICU setting. The model structure and features were similar to the aforementioned study of Austin and Anderson (1999), but the model was configured mainly with observed data from an American hospital and the model results were compared favourably with observation. The Monte Carlo technique was applied to simulate the stochastic process and multiple replications were performed to estimate the mean and confidence interval of model results; this has become the standard practice for subsequent studies when the model is treated stochastically. The model estimated that the basic reproduction number (i.e., the number of secondary transmissions cause by a typical primary case in a large population of susceptible patients) for VRE in the hospital was

approximately 3-4 without intervention and 0.7 when infection control measures were implemented.

Almost in parallel, Cooper *et al.* (1999) proposed a similar mathematical compartmental model to study the transmission of hand-borne HAIs in the hospital unit setting. Like the one proposed by Austin *et al.* (1999), the model explicitly considered both patients and HCWs and classified them as either colonised or uncolonised. Stochastic simulation with multiple replications was carried out to measure the effectiveness of various intervention policies under different scenarios. The intervention policies and influencing factors considered in the model include the transmissibility of the pathogen, the probability of colonisation on admission, patients' lengths of stay, hand-washing frequency and infection detection rate. Direct observed data were not applied to configure or validate the model. Among other findings, the study concluded that chance effects are likely to be the most important factor in determining the course of an outbreak in the hospital setting with a small patient population.

Lipsitch *et al*. (2000) appears to switch back the focus to the problem of antibiotic resistance. Two mathematical compartmental models were built to identify effective intervention polices to control HAIs and to reduce the antibiotic resistance of the pathogens. HCWs were not explicitly considered in the model. One model divided the patient into three compartments: susceptible, infected with sensitive strain and infected with resistant strain. The other model further divided each compartment into two sub-compartments depending on patients' antibiotic treatment history. The model was evaluated only deterministically. Several interesting and yet paradoxical conclusions were drawn from the model, e.g., the use of an antibiotic for which resistance is not yet present will be positively associated with the carriage of pathogen resistance to another antibiotic at the individual patient level, but negatively associated at the population level. The model was configured with data from other studies and the model predictions were compared with previously published data.

Bonten *et al.* (2001) summarised and reviewed some of these early HAI modelling studies. The review suggested that the use of mathematical modelling to understand the transmission dynamics of HAIs in the hospital setting was still in its early stages

and concluded several potential benefits of the modelling study: (1) models can provide a theoretical basic for evaluating interventions to control the infection transmission and the development of antibiotic resistance, (2) models can suggest explanations of observations that have not been explained yet, (3) models can help illustrate the range of stochastic variation and chance effects, and (4) models can suggest standards for the evaluation of alternative intervention policies.

Individual-based Models

Among the early studies to model HAIs, there is only one study that adopted individual-based modelling technique rather than the prevailing mathematical compartmental models. Along with one study (Sebille *et al*. 1997) which applied mathematical compartment model to study the transmission of nosocomial pathogens in a hospital ICU, Sebille and Valleron (1997) also applied an individual-based model to study the same subject in another paper. Most notably, compared to mathematical compartmental models, the model allowed for the representation of every individual patient and HCW. The authors argued that the model offered a new approach to model the spread of nosocomial pathogens in a hospital unit. The Monte Carlo technique was used to evaluate the model stochastically and the model, which consists of seven modules, was written in the C language.

Although the model adopted an individual-based modelling method, it did not fully use the potential of the different modelling paradigm and still had many restrictive assumptions associated with mathematical compartmental models. The model still assumed a constant number of patients and HCWs and 100% occupancy, and the length of stay was still assumed to follow an exponential distribution. The patients' locations and movements were not represented in the model. Both patients and HCWs had limited behaviour rules and only a few attributes which were considered by previous mathematical models. Furthermore, no direct observed data were applied to configure or validate the model. Nevertheless, this study is valuable in the sense that it is the first attempt to apply individual-based models to study HAIs.

Summary

Even though the number of studies was limited, these early studies give a comprehensive picture of the modelling of HAIs:

- In terms of modelling methods, although one study applied an individual-based model, most of these early studies adopted mathematical compartmental models which is still the dominant modelling method;
- Models can be treated both deterministically and stochastically. From these early studies, a trend which favours stochastic treatment through the Monte Carlo technique can be spotted;
- Regardless of individual-based or mathematical compartmental models, there are studies that do not explicitly represent HCWs while others do. The difference may affect the way the model is structured and the way the transmission of the pathogens is modelled;
- The scope of the model can be a single hospital unit (normally an ICU), the whole hospital or the hospital together with its community;
- The modelling exercise itself can be independent and separate from observed data, though studies do try to configure and validate the model using observed data when possible; and
- Early studies tend to focus on the problem of antibiotic resistance, however, the objectives of the study have gradually shifted to the evaluation of various intervention policies aiming to prevent and control HAIs.

2.3.2 Recent Developments

Mathematical Compartmental Models

Following the early studies, for a while, the focus of the HAI modelling study switched to the fitting of mathematical models to observed data to estimate the underlying transmission parameters. Grundmann *et al.* (2002) fitted a stochastic mathematical compartmental model to the MRSA observed data in a hospital adult ICU. The fitted model was then applied to evaluate the effectiveness of control policies of hand-washing, HCW-patient ratio and staff cohorting (i.e., grouping patients with a given infection in an isolated area and assigning dedicated staff). Pelupessy *et al.* (2002) also fitted a stochastic Markov model, which was based on previous mathematical compartmental models, to the observed data of two hospital pathogens, VRE and Pseudomonas aeruginosa, in a hospital ICU. The purpose of the model fitting was to evaluate the relative importance of two possible colonisation

routes: exogenous cross-transmission by HCWs and endogenous acquisition due to the use of antibiotics. Only patients, who were classified as either colonised or uncolonised, were explicitly represented in the model. Similarly, Cooper and Lipsitch (2004) applied a stochastic hidden Markov model to fit the observed data of three types of hospital pathogens: MRSA, VRE and Gram-negative rods. Key epidemiological parameters, such as the transmission rate and the endemic setting, were estimated by the model fitting process. The model classified patients as either colonised or uncolonised. Forrester *et al*. (2005) fitted a stochastic mathematical compartmental model to the observed data of MRSA in a hospital ICU. Like other model fitting studies, only patients were explicitly represented in the model. However, apart from colonised and uncolonised patients, isolation patients were also represented as a separate compartment in the model. The model assumed three sources of transmission: background contamination, non-isolated patients and isolated patients. The aim of the study was to quantify the transmission rates from these different sources.

A mathematical compartmental model was proposed by Cooper *et al.* (2004) which not only considered the hospital, but also the corresponding community. Only patients were explicitly represented in the model. Apart from colonised, uncolonised and isolated patients in the hospital, people in the community were also grouped into four compartments depending on their colonisation status and re-admission rate to the hospital. The model was evaluated mainly through stochastic Monte Carlo simulation technique. MRSA was the hospital pathogen under study and, for the first time, the effectiveness of isolation as an intervention policy was investigated. Due to the inclusion of the hospital community, the study revealed that although local interventions may control the spread of the pathogens successfully within the hospital in the short-term, the fact that potentially colonised patients can accumulate in the community reservoir and re-admit to the hospital multiple times may lead to long-term control failure.

Raboud *et al.* (2005) applied the model proposed by Austin and Anderson (1999) to study the transmission of MRSA in a hospital general medical ward using very detailed observed data. The model was evaluated using the Monte Carlo method, and the effectiveness of various intervention policies was evaluated. Most noticeably,

screening test as an intervention policy was evaluated and the study found that screening patients on admission can reduce MRSA transmission.

Bootsma *et al.* (2006) proposed what seems to be the most complicated mathematical compartmental model so far. The model comprised three hospitals and each hospital had 36 general wards and 5 ICUs. Both patients and HCWs were represented. Patients were classified as colonised, uncolonised or isolated, and a small proportion of colonised patients were further classified as "super-spreaders". There were two types of HCWs: one type only interacts with patients in the same hospital unit, while another type interacts with patients in the whole hospital. Regardless of the type, HCWs were classified as colonised or uncolonised. The community of each hospital was also represented in the model. The three-hospital model was evaluated by the Monte Carlo simulation while a single hospital model was evaluated deterministically by analytical methods. The model was applied to quantify the effectiveness of MRSA intervention policies, in particular a rapid screening test. Other interventions evaluated by the model include isolation upon detection, pre-emptive isolation, screening for suspected HCWs, ward closure and decolonisation treatment. Many of these intervention policies such as pre-emptive isolation, screening for HCWs and ward closure were considered for the first time. Noticeably, patient movements within the hospital were captured in the model. Observed data were applied to configure the model when possible. The study suggested strong causality between the S&D strategy and low MRSA prevalence.

Robotham *et al.* (2006) applied a stochastic mathematical compartmental model based on the one proposed by Cooper *et al.* (2004) to compare and investigate the impact of two screening strategies, random screening (i.e., screening patients randomly during their hospital stay) and admission screening, on controlling MRSA. Apart from the seven compartments in the original model, an additional compartment was included to represent patients who are detected as colonised with MRSA but unable to be isolated due to constrained isolation facilities. The model was configured with data from previous studies. The conclusion of the model was that screening strategies have a significant impact on controlling MRSA, and among the two screening strategies considered, random screening is more efficient than on admission screening.

Boldin *et al.* (2007) built a mathematical compartmental model to evaluate the relative effects of barrier precautions and topical antibiotic treatments on HAIs in the hospital ICU setting. HCWs were not represented in the model. The model considered both exogenous cross-transmission and endogenous within-host transmission between different parts of the body sites, including skin, gut and lungs, due to selective pressure. Therefore, besides uncolonised compartment, colonised patients were further divided into seven compartments depending on which part(s) of their body were colonised. No particular hospital pathogen was considered and no observed data were used to configure the model. The study suggested that routine use of topical antibiotics for infection control is not effective and should not be practiced.

The latest modelling study was conducted by McBryde *et al.* (2007). The authors applied a mathematical compartmental model not only to estimate the transmission rate of MRSA in a hospital ICU using observed data, but also to evaluate the effectiveness of various intervention interventions including hand-washing, decolonisation, HCW-patient ratio and cohorting. The model was based on many previous studies which explicitly represented patients and HCWs. A Bayesian framework, which allows the incorporation of unseen events such as the timing of actual MRSA transmission, was adopted to help quantify the transmission rate. The study concluded that, for the specific case study, MRSA was only sustained through the admission of new colonised patients since the ward reproduction number was below unity.

Individual-based Models

Probably the first modelling study applying individual-based model on HAIs was done by Sebille and Valleron (1997), and it is only about a decade later Hotchkiss *et al.* (2005) adopted the method again. They developed a spatially explicit discrete element model to study the transmission dynamics of HAIs in the hospital ICU setting. Each individual patient and HCW was represented in the model, and as a significant improvement compared to the previous individual-based model, each patient also had his/her own explicit location which was represented as a node of a two-dimensional lattice.

However, like the previous study, the model did not make full use of the potential advantages that the individual-based approach provides and still has many of the restrictive assumptions of the mathematical compartmental model. For example, although patients had their explicit locations, they still could not move within the hospital unit. The number of patients and HCWs were still constant and the ward occupancy was assumed to be always 100%. Each patient and HCW had very limited attributes and no behaviour rules were defined for the patients. The model was built based on a hypothetical ICU and therefore no observed data were applied. Some intervention polices were evaluated with the focus on HCW visiting and allocation rules which are difficult to be represented in mathematical models. The model was only run for a week which made it difficult to study long-term transmission dynamics.

Summary

Table 2.1 summaries previous literature on modelling HAIs. By reviewing all the literature, especially recent studies discussed in this section, some trends of HAI modelling are identified:

- The mathematical compartmental model is still the dominant method for modelling HAIs. There are different types of mathematical compartmental models. The classic ones, such as those proposed by Sebille *et al.* (1997) and Austin *et al.* (1999), normally classify patients and HCWs only as colonised or uncolonised. Recent studies have introduced more compartments which represent patients under isolation, patients in the community (Cooper *et al*. 2004), patients who are "super-spreaders", HCWs who serve patients in a single hospital unit and in the whole hospital (Bootsma *et al.* 2006) and patients colonised in different body site(s) (Boldin *et al.* 2007). Mathematical compartmental models were also evaluated in the form of Markov process which helps to fit the model to observed data to estimate key model parameters such as transmission rate (Pelupessy *et al.* 2002; Cooper and Lipsitch 2004). There are also advances in individual-based models, for example, individual patients can have their own spatial locations (Hotchkiss *et al.* 2005);
- For mathematical compartmental models, there seems to be no preference for explicitly representing HCWs in the model or otherwise. The choice depends

more on the assumptions made about the model and the availability of data. For the two identified individual-based models, it appears that modellers prefer to explicitly represent both HCWs and patients;

- Most modellers have developed stochastic models to accommodate the chance effects and randomness associated with the small patient population in the hospital setting;
- In terms of model scope, the trend appears to be that either the model focuses on a single hospital unit, normally an ICU, in more detail; or, if the model focuses on the whole hospital, the corresponding community is also modelled to represent the wider feedback mechanics (i.e., discharged colonised patients from the hospital gradually build up in the community reservoir and can be re-admitted to the hospital);
- Regarding model objectives, the focus of the model seems to be switched from competition between sensitive and resistant strains of the pathogen in the early days, to the fitting of the model with observed data to estimate the transmission rate, and then to the evaluation of the effectiveness of various intervention policies. There is also a clear trend that more studies are focusing on MRSA; and
- More studies seem to use observed data for both model configuration and validation.

Table 2.1 Summary of previous modelling studies on hospital-acquired infections

Author(s) (Year)	Modelling method	HCWs included?	Deterministic/ stochastic	Model scope	Infectious diseases under study	Observed data	Intervention policies evaluated
Massad *et al.* 1993	MCM (3)	No	Deterministic	Hospital	Sensitive and resistant strains of a pathogen	Observed data from other studies are used to configure and validate the model	No
Sebille *et al.* 1997	MCM (6)	Yes	Deterministic	Hospital ICU	Antibiotic-resistant pathogens like MRSA	No observed data	Yes (hand-washing, antibiotic policy and endemic setting)
Sebille and Valleron 1997	IBM	Yes	Stochastic	Hospital ICU	Antibiotic-resistant pathogens	No observed data	Yes (hand-washing)
Austin and Anderson 1999	MCM (4)	Yes	Deterministic/ Stochastic	Patient/Hospital/Hospital & Community	Antibiotic-resistant pathogens like MRSA and VRE	No observed data	Yes (hand-washing, HCW-patient ratio, and single and multiple drug treatment)
Austin *et al.* 1999	MCM (4)	Yes	Deterministic/ Stochastic	Hospital ICU	VRE	Observed data are used to configure and validate the model	Yes (hand-washing, cohorting and antibiotic treatment)
Cooper *et al.* 1999	MCM (4)	Yes	Deterministic/ Stochastic	Hospital unit	Hand-bore pathogens like MRSA	No observed data	Yes (transmissibility, endemic setting, length of stay, hand-washing and detection)
Lipsitch *et al.* 2000	MCM (3,6)	No	Deterministic	Hospital	Antibiotic-resistant pathogens	No observed data	Yes (antibiotic policy)
Grundmann *et al.* 2002	MCM (4)	Yes	Deterministic/ Stochastic	Hospital adult ICU	MRSA	Model is fitted to observed data	Yes (hand-washing, HCW-patient ratio and cohorting)
Pelupessy *et al.* 2002	MCM (2) (Markov	No	Deterministic/ Stochastic	Hospital ICU	VRE and Pseudomonas	Model is fitted to observed data	No

	process)				aeruginosa		
Cooper and Lipsitch 2004	MCM (2) (Markov process)	No	Deterministic/ Stochastic	Hospital unit	MRSA, VRE and Gram-negative rods	Model is fitted to observed data from other literature	No
Cooper *et al*. 2004	MCM (7)	No	Deterministic/ Stochastic	Hospital and its community	MRSA	Observed data are used to partially configure the model	Yes (isolation)
Forrester *et al.* 2005	MCM (4)	No	Deterministic/ Stochastic	Hospital ICU	MRSA	Model is fitted to observed data	No
Hotchkiss *et al.* 2005	IBM	Yes	Stochastic	Hospital ICU	Hospital pathogens	No observed data	Yes (transmissibility, hand-washing, cohorting and HCW allocation rules)
Raboud *et al.* 2005	MCM (4)	Yes	Stochastic	Hospital unit	MRSA	Observed data are used to configure the model	Yes (screening, staff workload and hand-washing)
Bootsma *et al.* 2006	MCM	Yes	Deterministic/ Stochastic	Hospital, and its community	MRSA	Observed data are used to configure the model	Yes (isolation, pre-emptive isolation, screening, screening for HCWs, ward closure and decolonisation)
Robotham *et al.* 2006	MCM (8)	No	Deterministic/ Stochastic	Hospital and its community	MRSA	No observed data	Yes (random and admission screening)
Boldin *et al.* 2007	MCM (8)	No	Deterministic/ Stochastic	Hospital ICU	Hospital pathogens	No observed data	Yes (barrier precautions and antibiotic treatment)
McBryde *et al.* 2007	MCM (4)	Yes	Deterministic/ Stochastic	Hospital ICU	MRSA	Observed data are used to configure the model	Yes (hand-washing, decolonisation, HCW-patient ratio and cohorting)

Remark: MCM (x) – Mathematical compartmental model (number of compartments); IBM – Individual-based model.

2.3.3 Conclusions

Compared to aggregate level mathematical compartmental models, there is clearly a lack of individual-based models to study HAIs. For the few available individual-based models, the literature review shows that they have not fully explored the benefits that individual models may provide (e.g., locations and movements of patients, complex interactions among patients) and still retain most of the restrictive assumptions associated with compartmental models, such as exponentially distributed lengths of stay, and constant and full ward occupancy. These assumptions can be relaxed by individual-based models and they are important to transmission dynamics of HAIs.

A range of intervention policies have been evaluated by existing modelling studies. For example, the policies of isolation and hand-washing have been extensively studied by many models. However, to combat HAIs such as MRSA, health authorities around the world (e.g., NHS in the UK) are adopting more aggressive intervention policies such as compulsory admission screening. Many clinical trials have been conducted in recent years to evaluate the effectiveness of admission and repeat screening, and rapid tests of MRSA (Harbarth *et al.* 2006; Cunningham *et al*. 2007; Hardy *et al*. 2007). Various decolonisation treatments have also been studied (Harbarth *et al*. 1999; Macfarlane 2007). Compared to traditional intervention policies, these rather novel intervention policies have not been fully represented and systematically evaluated by existing modelling studies.

In general, there is also a lack of validation of existing HAI models before they are applied to test different policies or make quantitative predictions. There is also potential to improve the experimental design methods adopted by previous modelling studies so that the effectiveness and robustness of intervention policies can be systematically evaluated. The thesis will try to fill in the gaps identified by the literature review and attempts to make a significant contribution to the subject.

2.4 Summary

This chapter has made necessary preparations for the rest of the thesis by providing a comprehensive literature review of existing HAIs models. The review suggested that

there is a lack of studies using individual-based models to study HAIs, especially if the model can relax some of the restrictive assumptions associated with aggregate-level models such as exponentially distributed lengths of stay and full ward occupancy. It is also worthwhile to embed new HAI prevention policies and technologies, such as rapid screening test and decolonisation treatment, in the model and to systematically evaluate the effectiveness of these interventions using formal experimental design methods. The overall objectives and research questions of the thesis will be derived from the findings and discussions in this chapter.

Chapter 3

Methodology

3.1 Introduction

The overall research objectives and questions of the thesis are derived based on previous chapters. The main purpose of the chapter is to explore the methodological issues of addressing these identified research questions. The key questions include the justification of ABS as a useful technique to the modelling and management of HAIs, the framework for applying ABS to the modelling of HAIs and the building of a MRSA model based on an empirical study, and the evaluation of intervention policies using the MRSA model.

3.2 Research Objectives and Questions

Chapter 1 and 2 have identified the gaps in previous studies and the key motivations of this thesis. HAIs are a major threat to patients in the hospital and have placed a heavy burden on public health authorities around the world. Various intervention polices are available to prevent and control HAIs and these policies have been investigated by clinical research and some of them have been evaluated by modelling studies. However, there are still many problem areas facing the management of HAIs, especially the evaluation of new technologies and intervention polices developed to control the spread of infections.

It has been demonstrated in literature review that no well-developed ABS models have been built to study HAIs. The introduction of ABS and its application to the modelling of infectious diseases indicates that ABS, as an individual-based and bottom-up modelling approach, may have a number of advantages to the modelling of HAIs.

The empirical MRSA case study in the Birmingham Heartland Hospital provides valuable source of observed data which can be used for both model configuration and validation. Due to the empirical elements of the model, the model experimentation results may be more dependable to advise real world management policies to combat MRSA, especially if reasonable level of confidence can be placed on the model through the model validation process. In particular, the effectiveness and robustness of various intervention policies determined by the model may be of great value to the management of HAIs.

Despite of the MRSA empirical study, the thesis aims to provide a general framework for applying ABS to study of HAIs. The methodology and the proposed framework will not only guide the building of the empirical MRSA model, but also can be potentially applied to any types of HAIs (e.g., *C. difficile*).

The specific research objectives and questions that this thesis aims to answer are identified next (in Section 3.2.1 and 3.2.2 respectively).

3.2.1 Research Objectives

1. Agent-based simulation as a decision supporting tool to the modelling and management of hospital-acquired infections

To investigate the feasibility and value of using agent-based simulation to provide a flexible and robust modelling approach to the support of modelling and management of hospital-acquired infections.

2. Application of agent-based simulation to the modelling and management of hospital-acquired infections

To provide a general framework of applying agent-based simulation to the modelling and management of hospital-acquired infections.

To test and validate the use of agent-based simulation model on a MRSA study.

3. MRSA infection control in the hospital

To quantify the effectiveness and test the robustness of various MRSA intervention policies and summarise the indications to the management of MRSA in the hospital setting.

3.2.2 Research Questions

1. Agent-based simulation as a decision supporting tool to the modelling and management of hospital-acquired infections

Whether, why, and when agent-based simulation is a useful technique to the modelling and management of hospital-acquired infections?

2. Application of agent-based simulation to the modelling and management of hospital-acquired infections

How agent-based simulation can be applied as a general framework to the modelling and management of hospital-acquired infections?

How agent-based simulation can be applied to model a MRSA study and be properly validated?

3. MRSA infection control in the hospital

How to quantify the effectiveness of various MRSA intervention polices and how robust are these intervention polices considering various influencing factors? What are the indications to the management of MRSA in hospital setting?

3.3 Potential Methods for Modelling Healthcare-acquired Infections

In this section, a taxonomy of potential methods to model HAIs will be proposed. The modelling techniques considered not only include those that have already been applied, but also those that have not (e.g., ABS, DES and SD). The taxonomy will provide a basis to compare the advantages and disadvantages of ABS relative to other methods regarding HAI modelling (see Section 3.4).

Brennan *et al.* (2006) evaluated and classified a range of modelling and simulation approaches in the context of health economics and disease modelling. In the

taxonomy, they created a matrix and broadly classified all models as cohort/aggregate level models and individual level models from the horizontal direction, and models where no interaction is allowed and models where interaction is allowed from the vertical direction. Cohort/aggregate models do not represent individual patients explicitly and only consider patients in homogenously mixing groups/cohorts. Individual-based models, on the other hand, explicitly represent each heterogeneous individual patient. Regarding time, models were also classified as either untimed or timed which can be further labelled as either discrete or continuous time. The framework is used to assist the discussion of potential methods for modelling HAIs.

In order to describe the transmission dynamics of HAIs, the modelling methods need to meet two fundamental requirements. Firstly, time, either continuous or discrete, needs to be reflected by the modelling method. Secondly, the method needs to have the ability to represent interactions, either among patients or HCWs themselves or between patients and HCWs. As a result, the potential methods to model HAIs can be narrowed down to the timed models where interaction is allowed (see Figure 3.1). The literature review in Section 2.3 shows that most existing models are mathematical compartmental models, which belong to cohort/aggregate models, while few are individual-based models. This dichotomy will guide the following discussions.

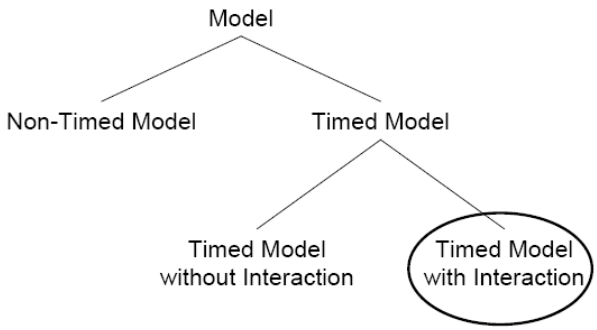

Figure 3.1 Potential methods for modelling hospital-acquired infections

3.3.1 Cohort/aggregate Models

Mathematical Compartmental Models and Markov Models

Most existing HAI models are cohort/aggregate models in the form of mathematical compartmental models or the corresponding Markov models. In compartmental models, patients and HCWs are divided into different groups or compartments,

normally regarding their colonisation status (e.g., colonised, susceptible) and other risk factors (e.g., isolated). People in each compartment have no identity and are assumed to be homogenous, and the model only considers the total number of individuals in each compartment. Mathematical equations based on epidemiological and biological rules are used to govern the flow rate between compartments. For example, according to the mass action assumption, the rate of new secondary cases (i.e., the number of individuals flow from susceptible to colonised compartment) is proportional to the product of the number of susceptible and colonised patients. These mathematical equations determine the dynamics of the model and the number of individuals in each compartment through time, and collectively they can be described as a system of ordinary differential equations.

The compartmental models can be evaluated deterministically by finding analytical solutions from the ordinary differential equations or the steady state of the corresponding Markov model. When models are too complex to be mathematically tractable, they can be treated deterministically by numerical methods. Increasingly, the compartmental models are evaluated stochastically, either by analytical techniques for simple stochastic processes or, in most cases, by numerical simulation applying the Monte Carlo technique, i.e., the application of random numbers. Table 3.1 summarises the potential HAIs modelling methods belong to cohort/aggregate models.

System Dynamics

SD is a simulation method which has been widely used in the business and management domain (Forrester 1958; Sterman 2000). Mathematically, SD may be represented as a set of differential equations. SD models seldom have analytical solutions and are always evaluated numerically through simulation. Classical epidemiological models, such as susceptible-infected-removed (SIR) model, can be easily represented and solved as SD models (Murray 2002). SD also has been used to study the complex transmission dynamics and the cost-effectiveness of interventions of community-based infections such as *Chlamydia* which is a type of sexually transmission infection (Evenden *et al.* 2005; Brailsford 2007). However, it seems that SD has never been applied to model the transmission of HAIs. A possible reason is that SD models are normally evaluated deterministically which may not be appropriate to model a small patient population in the hospital setting.

In a SD infection transmission model, homogeneous individuals are grouped together and represented as levels/stocks (which correspond to compartments in mathematical models); and infection transmission or recovery is represented as the transition or flow to and from different levels/stocks.

3.3.2 Individual-based Model

There are some common properties for individual-based models which may be applied to study HAIs. These shared properties include:

- The capability of representing both time and interactions;
- Patients and HCWs are explicitly represented as heterogeneous individuals;
- Individual patient or HCW has multiple attributes and states and the change of state from one to another is stochastic or probabilistic in nature; and
- Models are normally evaluated stochastically by numerical simulation using the Monte Carlo technique, and multiple replications are performed to estimate the mean model outputs.

A further breakdown of the types of individual-based models can be troublesome since different definitions and interpretations may exist for agent-based modelling/simulation (see Section 1.3.1), DES and individual-based models. For example, in one paper, agent-based models were considered the same as discrete element models (Hotchkiss *et al.* 2005) which, in essence, represent general individual-based models. In another paper, the authors classified their model as individual-based modelling without further clarification of the type of individual-based models (Sebille and Valleron 1997). Also, most modellers seem to use ABS and agent-based modelling, and individual-based simulation and individual-based modelling interchangeably.

Discrete-event Simulation

DES concerns the modelling of a system as it evolves over time by a representation in which the state variables change instantaneously at separate points of time (Law 2007). DES, as its name suggests, maintains a future event list and have the capability of event scheduling. Two principal approaches have been suggested for advancing the

simulation through time: next-event time advance (event-driven) and fixed-increment time advance (time-slicing). For next-event time advance, the simulation is always advanced to the time of the most imminent event in the future event lists, then the state of the system and the future event lists are updated. For fixed-increment time advance approach, simulation clock is advanced in increments of exactly Δt time units and a check is made to determine if any events should have occurred during the previous interval of length Δt.

Conventionally, DES is normally applied to systems that can be regarded as a queuing system where entities go through the system consists of multiple activities, being served at each activity by scarce resources, and need to wait in a queue between each activity if necessary. Typical queuing systems include production line, airport, banks, restaurants, call centres, accident and emergency departments of hospitals and etc. In HAI modelling, patients may correspond to entities in DES and the disease development may be represented as discrete activities with unconstrained resources (e.g., there is no queue between each activity). The heterogeneity nature of individual patient can be represented by various attributes associated with each entity. The different values of these attributes may affect the way a patient entity passes through the disease development stages.

DES has been applied to study community-based infections. For example, McKenzie *et al.* (1998) applied DES to study the transmission of malaria. The development of the parasite in both hosts (i.e., humans) and vectors (i.e., female mosquitoes) and the interactions between hosts and vectors were represented in the model. Allore *et al.* (1998) used DES to study the effectiveness of mastitis control in dairy herds (i.e., cows). Part of the model was to represent the infection transmission among the cow population using DES. Cohen *et al.* (2000) proposed a DES model to represent the transmission of feline herpes virus within the cat population. Each individual cat was associated with a range of attributes that may affect the transmission. The social and spatial structure of the cat population was also described by the model. Rauner *et al.* (2005) applied DES to evaluate and compare two alternative strategies for the prevention of mother-to-child transmission of HIV in developing countries. DES was chosen over decision tree models and SD models as each mother-baby pair can be tracked and individual variability can be represented. However, it appears that DES

has not been applied to study transmission dynamics in the hospital setting (see Section 2.3).

Classification of Individual-based Models

An attempt is made to breakdown the types of individual-based modelling methods from the perspective of ABS (see Figure 3.2). In this classification, ABS has both a broader sense and a narrow sense. In the broader sense, ABS is the same as individual-based models as long as the model meets the aforementioned shared properties. On the other hand, ABS in the narrow sense refers to what is generally known as ABS where a bottom-up, rather than top-down, modelling approach is adopted and agents have rather complex behaviour rules (see Section 1.3). The term ABS will only refer to its narrow sense hereafter.

Any individual-based models that can not be classified as ABS (in the narrow sense) or DES will be labelled as general individual-based models. The general individual-based models are not event-driven, otherwise they may be classified as DES. The individuals in these models do not have complex behaviour rules and models are not built around individuals using a bottom-up modelling approach, otherwise they can be classified as ABS.

In the broader sense, individual-based models share common features among themselves. Firstly, they all have the aforementioned common properties. Then, ABS and DES share some characteristics such as they can both incorporate event-scheduling capability, and both modelling methods have established methodology and standard computer packages. ABS and general individual-based models may share features such as a time-slicing mechanism. Finally, DES and general individual-based models may share the properties of being a top-down modelling approach.

Each type of the individual-based modelling method has its own distinctive features. In ABS, the model is built around agents who, apart from multiple attributes and states, may have complex behaviour rules and can be proactive, adaptive and intelligent. Moreover, unlike other individual-based modelling methods, ABS adopts a bottom-up modelling approach from the perspective of the locally defined agents. In DES, individuals are represented as entities which are only one of the many elements

of the model and normally pass through a predefined queuing system consists of queues and workstations. Entities in DES can have multiple attributes but normally only have limited rules. For general individual-based models, there is no established methodology or standard computer packages; instead, models are normally developed in general-purpose languages in which passive individuals change their states according to pre-defined rules. The relationships among different types of individual-based models are shown in Figure 3.2.

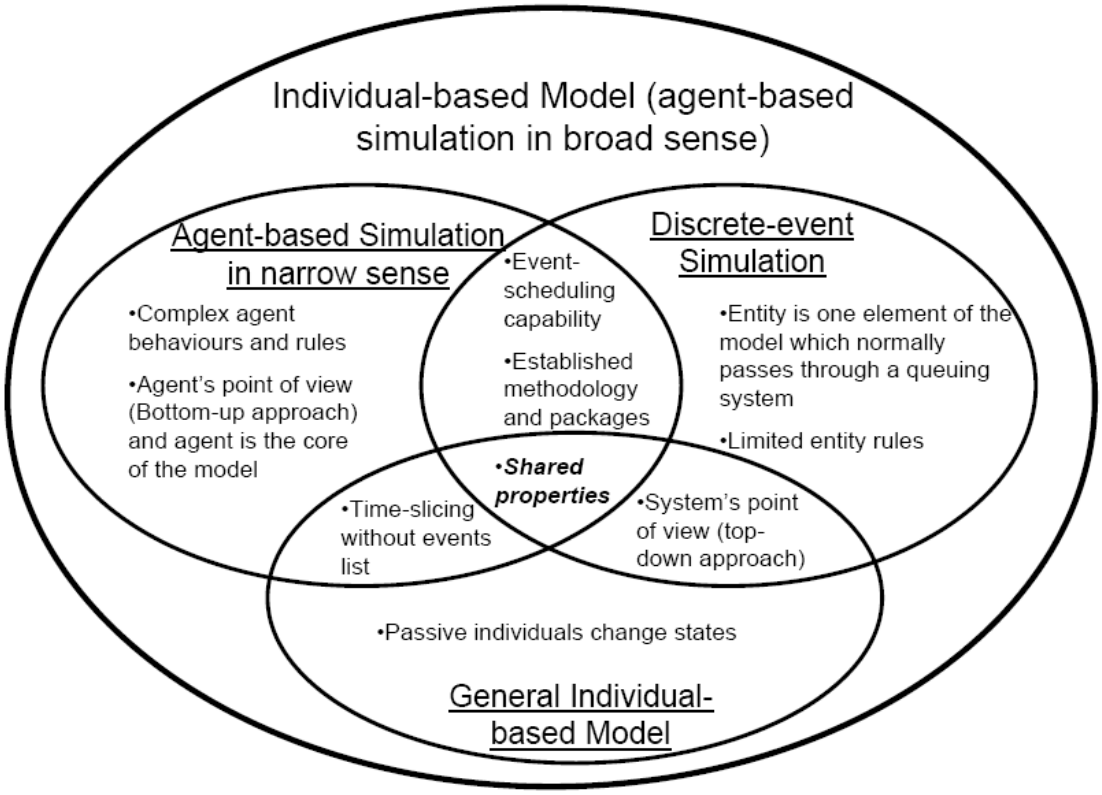

Figure 3.2 Relationships of different individual-based modelling methods

Individual-based models are normally only treated stochastically by numerical simulation through the Monte Carlo technique. It is possible to evaluate individual-based models deterministically in theory (i.e., simulation with no random numbers), but such practice is seldom performed as it has limited practical values. DES and ABS both have standard techniques and computer packages to aid model developments and experimentations. Table 3.1 summarises the potential methods, both cohort/aggregate level and individual level models, for modelling HAIs.

Table 3.1 Summary of methods for modelling hospital-acquired infections

	Cohort/aggregate level model		Individual level model		
	Mathematical	compartmental	General	DES	ABS

		model (Markov model) / SD	individual-based model		
Deterministic	Analytical	Solving system of ordinary differential equations or finding stead state for Markov model.	Not applicable.		
	Numerical	Simulating differential equations or Markov model with no random number (system dynamics).	Possible in theory, but with limited practical values.		
Stochastic	Analytical	Analytical solution for stochastic Markov process.	Not applicable.		
	Numerical	Simulating Markov process using the Monte Carlo technique.	Simulation using the Monte Carlo technique.	Standard simulation techniques and packages.	

According to this classification, previous individual-based models (Sebille and Valleron 1997; Hotchkiss *et al.* 2005) should be labelled as general individual-based models. These models have passive individual patients and HCWs who change their states according to pre-defined rules through time. They are not ABS models in the narrow sense since (1) they have not adopted a bottom-up modelling approach from the patient's and HCW's perspective, (2) individuals have no complex behaviour rules, and (3) they have not followed an established methodology which exists for ABS. At the same time, they are also not DES since both models have no event-scheduling capability.

3.4 Comparison between Agent-based Simulation and other Modelling Methods

The comparison between ABS and other modelling methods will be performed under the taxonomy proposed in the previous section.

3.4.1 Comparison between Individual-based Models and Cohort/Aggregate Models

Under the proposed taxonomy, cohort/aggregate level models include discrete and continuous Markov models, mathematical compartmental models and SD, either evaluated deterministically or stochastically. The following comparison between individual-based and cohort/aggregate models also applies to the comparison between

ABS and cohort/aggregate models, as ABS is one type of individual-based models. The comparison between ABS and other types of individual-based models will be discussed in detail in Section 3.4.2.

Relative Advantages of Individual-based Models

Flexibility to represent patient's attributes, risk factors and states

In individual-based models, each patient can be easily associated with a number of attributes and risk factors (e.g., age, sex, length of stay, type of disease, the number of wounds) that may affect the transmission of the HAI under study. Each individual patient and HCW can also have a number of states (e.g., colonised and susceptible). The change of state and the way a patient's attributes and risk factors affect transmission are modelled on an individual basis. Cohort/aggregate models normally can only handle a limited number of risk factors and states by dividing patients into different groups. As the number of risk factors and states increase, the required number of compartments may increase exponentially and soon become intractable. This problem of cohort/aggregate models is referred to by many authors as the "curse of dimensionality" (see for example Brennan *et al.* 2006).

The ability to represent spatial location and individual movement

One advantage of individual-based model is its ability to easily represent spatial location and the movements of patients and HCWs which has been demonstrated in the work of Hotchkiss *et al.* (2005). The location may be represented as a patient state and the movement is effectively the change of the state. In cohort/aggregate models, it may be troublesome to represent these features due to the "curse of dimensionality".

Less restrictive assumptions to suit underlying mathematics

Individual-based models, compared to cohort/aggregate level models, have less restrictive assumptions to meet the requirements of underlying mathematics. For example, in individual-based models, patients can be admitted and discharged following their own paths and consequently the total number of patients in the system and the ward occupancy may vary over time. On the other hand, most cohort/aggregate models assume a fixed patient population and a constant 100% ward occupancy.

Individual-based models can apply any types of parametric or empirical distributions to represent the length of stay while cohort/aggregate models need to assume exponentially-distributed length of stay. Such an assumption may be unrealistic since a large number of very short stays are expected which may not match the reality. Hospital length of stay has not been found to fit any simple parametric distribution, often because of a long tail of long stay patients.

Ability to represent sufficient detail and complexity

Cooper (2007) recognised that there will be an increase use of HAIs models as precision tools for probing the fine structure of detailed data sets. Individual-based models have much greater ability to represent detailed structure and incorporate complexity. For example, complex intervention policies, such as HCW allocation rules (Hotchkiss *et al.* 2005), admission coupled with repeat screening tests and decolonisation treatments, can be easily embedded in individual-based models. In contrast, one of the major difficulties with cohort/aggregate models is the rapid growth of mathematical complexity of the systems used to describe the various aspects of phenomena in sufficient detail (Bagni *et al.* 2002).

Reliable to make quantitative predictions

Compared to cohort/aggregate level models, since individual-based models are generally more representative of the real-world situation and have less restrictive assumptions, they are expected to be more reliable to make quantitative predictions. Cooper *et al.* (2007) suggested that most of the cohort/aggregate models use simple models that have permitted qualitative but not reliable quantitative predictions about the likely effect of different interventions.

Transparency and easily understood

Individual-based models can be more transparent and easier to understand than cohort/aggregate models, especially for people who do not have much mathematical background. Individual-based models normally do not have complex mathematical equations and expressions. Instead, the model structure and assumptions are described by narrative texts and diagrams, and the model dynamics are described through algorithms and rules which are similar to human language. Specific individual-based model types, such as ABS and DES, have their own tools (e.g., visual animation, flow

diagrams and state-charts) to aid the communication of the model with the audience. For cohort/aggregate models, the mathematical expressions and manipulations of these expressions to analyse the model, while may be easily understood and deemed rigorous and elegant, may be prohibitive to many people interested in HAI modelling study but with less mathematical background.

The ability to collect individual-level statistics

Since patients are individually represented and (potentially) tracked in individual-based models, it is possible to collect individual-level statistics and extract episode history of a specific patient, especially those who acquire colonisation during the hospital stay. Such individual-level statistics (e.g., the time of colonisation, the time of recovery and the associated risk factors) and episode information, which are not possible to obtain from cohort/aggregate models, can provide valuable information to study the detailed transmission dynamics of HAIs.

Relative Disadvantages of individual-based Models

Compared to cohort/aggregate models, there are also some relative disadvantages of individual-based models.

No rigorous mathematical expressions and loss of analytical power

Individual-based models normally do not have formal and rigorous mathematical expressions for model description and analysis. Therefore, it may not be possible to obtain analytical solutions from individual-based models. On the other hand, cohort/aggregate models may be written as a system of ordinary differential equations, in the form of Markov processes or by other mathematical expressions, and rigorous and precise solutions may be found for some simple cohort/aggregate models.

Less parsimonious and data demanding

While it is easy to incorporate heterogeneity and complexity into individual-based models, they can, for the same reason, be less parsimonious than cohort/aggregate models which normally only concentrate on a few important factors and relationships. Due to the same reason, individual-based models may need more data for model configuration and validation than cohort/aggregate models.

More time for model coding and verification

One indispensable step for developing individual-based models is to code and verify the model in a computer, which involves correctly transferring the conceptual model to a computer and making sure it works properly as expected. For complex models, these steps may take considerable time and effort. For cohort/aggregate models, model coding and verification are not necessary if the models are only evaluated deterministically via analytical methods. Many user-friendly off-the-shelf computer packages exist (e.g., Simu8® and Anylogic®) for certain type of individual-based models such as DES and ABS. Therefore, the time required to code and verify the model can be significantly reduced if the modeller is familiar with these packages.

Relative slow running speed

When models are evaluated numerically by computer simulation, individual-based models normally have a slower running speed compared to cohort/aggregate models since each individual needs to be explicitly represented, tracked and updated, and multiple replications are needed to estimate the mean model responses. The computing effort increases with the increasing number of individuals and the complexity of the model structure. The speed is normally not a problem since there are only a limited number of patients and HCWs in the hospital setting. However, if the community is to be included in individual-based models, the issue of running speed may become a problem. The rapid development of computer hardware and the technology of distributed computing may partially solve the problem. For example, Parker (2007) developed a framework for large-scale, distributed agent-based epidemic model which is capable of easily simulating millions of agents. Another way to tackle the problem is to combine the two modelling paradigms by representing the community using the cohort/aggregate model while retaining the individual-based model to represent the patients and HCWs.

3.4.2 Comparison between Agent-based Simulation and Discrete-event Simulation

Both ABS and DES have been applied to study community-based infection transmissions but not transmission dynamics in the hospital setting (see Section 1.3.4 and Section 3.3.2). However, according to the proposed taxonomy, they are both

potential methods of modelling HAIs (see Section 3.3.2). ABS and DES are similar simulation techniques in many ways. For example, they both model individuals who change states over time. Individuals in both types of models may have attributes and states, and the individual characteristics will affect the state change of that particular entity (in DES) or agent (in ABS). Event-driven time advance mechanisms may be applied to both techniques. Despite the similarities, ABS and DES are two simulation methods which have many different features and these differences may affect their suitability and ability to model certain systems. There has been no systematic study to compare the two simulation techniques in the context of HAI modelling. In this section, the differences between the two simulation methods and the advantages and disadvantages of ABS relative to DES are discussed in this context.

Differences between Agent-based Simulation and Discrete-event Simulation

ABS and DES have different origins and for a long time they have been studied in different disciplines. ABS is traditionally associated with artificial intelligence and complex adaptive systems (North and Macal 2007) while DES is traditionally associated with operational research. It is only until recently that ABS is gradually assimilated by the operational research discipline. From the perspective of DES, many ABS models maintain a future events list and have the capability of event scheduling. From the perspective of ABS, many DES models, especially those involve humans and interactions, look similar to ABS models where agents are not fully developed and have limited behaviour rules. In order to compare the two simulation methods in the context of HAI modelling, the differences between the two techniques are discussed first.

Modelling approach and the role of entity/agent

ABS adopts a bottom-up modelling approach from the agent's point of view and the agent is the single most important element of the model. DES adopts a top-down modelling approach from the overall system's point of view and the entity is only one of the many essential elements of the model.

Entity/Agent representation and dynamics

Apart from attributes, agents in ABS can have complex states and adaptive behaviour rules. Agents may change the states reactively or proactively. Agents' actual

development and movement routes may be unpredictable and broadly defined by boundaries or rules. In DES, simple attributes, numerical, text or logical, are attached to entities. Entities normally change their states only passively and pass through the pre-defined system structure.

Traceability and control of entity/agent

In ABS, the agent is the core of the model and normally it is easy to trace a particular agent at any time during the simulation. Consequently, the control of an agent is direct and can be carried out at any time. While in DES, it may not be easy to trace an individual entity once it enters the system. Therefore, the control of an entity is indirect and is normally performed only when an event happens to the entity (e.g., enter or leave a queue/activity).

Events generation

Since the agent is the core of ABS and it is easily traceable and directly controllable, events in ABS can be generated by agents themselves and naturally associated with any specific agent. In DES, events are normally generated by and associated with other model elements (e.g., queues and activities) which constitute the model structure. As a result, it is difficult to associate events with a specific entity.

Handling of a number of concurrent state changes

In ABS, the model is built around agents and the focus of the model is to describe agents' behaviour rules that change their states. Agents can be effectively and efficiently involved in a number of concurrent or simultaneous state changes. For example, the agent can change their states regarding spatial locations, and at the same time change states regarding the development of the infectious disease. If necessary, the patient agent can also be involved in other state changes that are relevant to the transmissions dynamics, such as the development of the underling illness and the aging process. The handling of a number of concurrent state changes can be easily implemented in ABS.

In contrast, DES normally assumes that each entity is only involved in a unique stream of activities of state changes which is embedded in the pre-defined model structure. It is difficult for entities to experience a number of simultaneous state

changes in most DES software. Davies *et al.* (1993) developed a structure which overcomes this problem. The approach allows an entity to engage in different concurrent activities or wait in any number of queues, and activities can be de-scheduled, interrupted or delayed. The advantages of the approach in the health context were described by Davies and Davies (1994) and the method is referred to as POST (patient-oriented simulation technique). The approach has been applied in many healthcare areas (Davies *et al.* 2000; Cooper *et al.* 2002) including the transmission of community-based infections (Rauner *et al.* 2005). POST was coded in Pascal and subsequently in Delphi (Cooper *et al*. 2008) and is not easy to use. Similar facilities are not available in commercial software.

Spatial and movement representation

ABS models are normally spatially explicit and this is one of the reasons that modellers adopt ABS. It is common for agents to move freely (within boundary and according to rules) and be aware of its own as well as other agents locations. In DES, in order to represent spatial location and movements, a pre-defined model structure and states which represent physical locations are needed. However, the inclusion of the movement activity may prohibit the entity from engaging in other activities in DES (see the previous section on handling concurrent state changes).

Exchange messages

Sending and receiving messages are standard techniques adopted by ABS and agents can act accordingly based on the information received from other agents or from the system environment. In DES, it is normally difficult to exchange messages between specific entities due to the difficulty to trace and directly control individual entities.

Application domain

ABS best suits those systems which consist of autonomous agents who interact with each other and with the environment. Infection transmission among patients and HCWs in the hospital setting is a good example of such a system. DES, on the other hand, is best for modelling queuing systems. The differences between ABS and DES are summarised in Table 3.2.

Table 3.2 Differences between agent-based simulation and discrete-event simulation

	Agent-based simulation	Discrete-event simulation
Modelling approach and the role of entity/agent	Bottom-up modelling approach from the agent's point of view. Agent is the most important element of the model.	Top-down modelling approach from the system's point of view. Entity is only one of the many essential elements of the model.
Entity/agent representation and dynamics	Agent can have complex states and behaviour rules and changes its states reactively or proactively. Agents' actual development and movement routes may be unpredictable and defined by boundaries or rules.	Simple attributes (numerical or text) are attached to entities. Entity changes its states only passively and passes through a pre-defined system structure.
Traceability and control of entity/agent	It is easy to trace a particular agent at any time during the simulation; Control of agent is direct and can be carried out at any time.	It is difficult to trace individual entity once it enters the system; control of an entity is indirect and is normally performed only when an event happens to the entity.
Events generation	Events can be generated by agents themselves and therefore can be naturally associated with the agent who creates the event.	Events are normally generated by and associated with queues or activities, and difficult to be associated with a specific entity.
Handling concurrent state changes	Agents can effectively and efficiently handle a number of concurrent state changes which are embedded within the agent.	Entities can normally only handle one stream of activity which is embedded in the predefined modelling structure.
Spatial and movement representation	It is common for agents to move freely (within boundary and according to rules) and be aware of its own and other agents' locations.	Entities can move within pre-defined states which represent physical locations. This may cause problems for other activities.
Exchange messages	Agents can exchange messages with each other and with the environment.	Entities can not exchange messages easily.
Application domain	Systems consist of autonomous agents who interact with each other and with the environment.	Queuing systems.

Relative Advantages of Agent-based Simulation

Based on the differences identified between ABS and DES, the relative advantages of ABS compared to DES can be summarised in the context of HAI modelling.

Natural choice to represent patients and infection transmissions

In general, compared to DES, ABS is a more natural choice to represent patients and infection transmission dynamics. In HAI models, patients are undoubtedly the most important element of the model. This is in line with the fact that agents in ABS are the core of the model. Furthermore, infection transmission occurs through the interactions among patients and between patients and HCWs; while ABS is deemed as most appropriate to model systems consisting of autonomous agents interacting with each other and with the environment.

Powerful tools to represent patient behaviour rules

Besides simple attributes and states, patients may have complex behaviour rules governing their infection development, movements and other aspects of state changes and activities. Compared to DES, ABS has more powerful tools to represent these behaviour rules, which can be further facilitated by the message exchange capability. For example, a patient's behaviour may be triggered by the information received from other patients or HCWs.

Powerful tools to represent patient spatial location and movement

One particular advantages of ABS, compared to DES, is its ability to represent patients' spatial locations and movements. The relative spatial location between susceptible and colonised patients may be critical to the successful transmission of a pathogen in the hospital setting. It is expected that the closer the two patients stay, the more likely contacts and consequently successfully transmissions may occur. ABS simulation has well established methods to represent spatial locations and various rules to govern the movements of agents.

Powerful tools to represent multiple concurrent state changes

Patients may have multiple concurrent state changes at the same time regarding infection development, detection status, decolonisation status, location and etc. Compared to DES, ABS is more straightforward to handle such situations.

Relative Disadvantages of Agent-based Simulation

The relative disadvantages of ABS compared DES include:

- Compared to DES which has a wide range of well-developed and user-friendly software packages, there are only a few software packages that support ABS and most of these have a relatively short history and are less user-friendly to develop, debug and implement ABS models. This may be a disadvantage for potential modellers when choosing between ABS and DES.
- Compared to DES, ABS is less effective in representing queuing systems which can be an important aspect of the HAI models when the patient pathway needs to be modelled.

3.4.3 Comparison between Agent-based Simulation and General Individual-based Models

The relative advantages of ABS compared to DES also apply to the comparison with general individual-based models. Furthermore, another relative advantage of ABS (and DES), compared to general individual-based models, is that both ABS and DES have well established methodology and both methods, especially DES, have well-developed computer packages while general individual-based models are normally built in general purpose computer languages such as Java and C++. The relative advantage of general individual-based models is that no prior knowledge about ABS (or DES) is necessary which may mean a shorter learning curve, especially if the modeller is proficient in general computer languages.

3.5 Model Structure

ABS models normally have a hierarchical model structure, with higher level representing system environment where agents stay, and lower level representing individual agents, their attributes, states, behaviours, and their interactions with each other and with the environment (Gilbert and Terna 2000). In the context of modelling HAIs, the corresponding system environment is either a hospital or a particular hospital unit (e.g., surgical ward, ICU) depending on the scale of the study. The

corresponding individual agents may include patients, HCWs and other humans/objects (e.g., visitors) depending on model assumptions.

In the hospital or hospital unit level of the model, global variables and other modelling constructs may be used to define the following aspects of the system environment:

- Capacity and layout of the hospital and/or hospital unit. For example, Figure 3.3 illustrates a typical hospital ward which has 22 beds in total, with 5 beds in single-bed rooms, 2 beds in a room/bay of 2 beds, and 15 beds in rooms/bays of 3 beds;
- Intervention policies. For example, in order to describe the screening test, the turnaround time, sensitivity and specificity of the screening test may need to be defined in the system environment level. Intervention policies and how they can be incorporated into the model are described in detail in Section 3.8.1;
- Global influencing factors. For example, the endemic setting and the transmission coefficient need to be defined globally. Influencing factors and how they can be incorporated into the model are described in detail in Section 3.8.2; and
- Other hospital and/or hospital-unit level parameters which are may be relevant to the modelling of HAIs, e.g., the admission rate of patients.

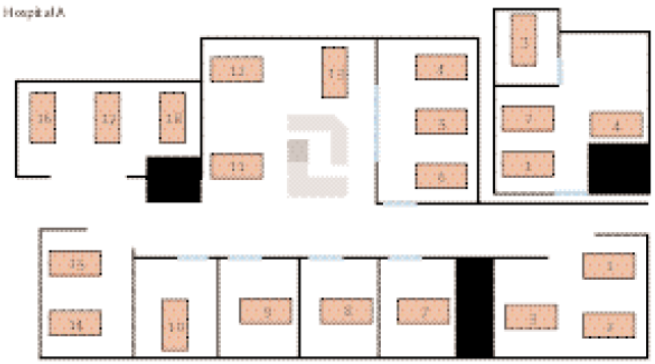

Figure 3.3 Layout of a typical hospital unit with 22 beds (Source: Cepeda et al. 2005)

The representation of agents in the lower level of the model will be discussed in detail in Section 3.6. The attributes and states of the agents are normally straightforward to define. However, behaviour rules, especially complex rules, may not be represented by simple variables, but need more sophisticated modelling constructs such as state-

charts, message exchange mechanisms and tailor-made computer language scripts. For example, in Anylogic®, which is one of the few commercially available ABS packages, the state-chart can define multiple concurrent state changes of a patient in terms of colonisation, location and etc. Behaviour rules and interactions can be embedded in the state-chart by pre-defined functions, message exchange mechanisms and java scripts.

3.6 Representation of Agents

The most important element of an ABS model is the agent and this section will describe the types of agents and the main issues for defining the patient agents.

3.6.1 Types of Agents

In the context of HAI modelling, agents are mainly patients, which are indispensable in modelling infection transmission, and HCWs, which may or may not be represented in the model. Unlike normal human beings represented by ABS models, patients are the recipients of the healthcare service and their actions and behaviours are largely confined by their patient identity and the regulations of the hospitals. Therefore, the behaviour rules of the patient agents will be predominantly reactive rather than proactive. HCW agents, if explicitly represented in the model, may have proactive behaviour rules since they are actively in charge of the provision of healthcare services to the patients.

3.6.2 Representation of Patient Agent

Patient is undoubtedly the most important agent in a HAI model since patients are both sources and recipients of infectious diseases in the hospital setting. In order to represent patient agents in ABS, their attributes (e.g., age, length of stay), states (e.g., colonised/uncolonised, location) and behaviour rules (e.g., admission/discharge, infection transmission) that govern the state changes need to be defined.

Lengths of Stay

Length of stay is probably the most important attribute of a patient when modelling infection transmission in the hospital. Length of stay will directly affect how long a

susceptible patient is exposed to transmission risk and how long a colonised patient exposes the risk to other susceptible patients. Length of stay may potentially interact with many intervention policies that aim to control HAIs (e.g., screening tests, decolonisation treatment).

ABS is able to apply any types of parametric and empirical distributions to represent the patients' lengths of stay (see Section 3.4.1). If necessary, patients may be divided into sub-groups each of which can have their own distribution. Both empirical and theoretical studies show that longer length of stay is positively correlated with the risk of colonisation (Morrison and Stolarek 2000; Cosgrove *et al.* 2005).

In general, empirical distribution based on observed data may be applied when validating the model against the actual situation. While a parametric distribution is preferred for model experimentation since they can be easily manipulated in terms of mean and shape.

In ABS, length of stay can be sampled from the selected distribution using random numbers when the patient agent is created. The patient will be discharged from the hospital when sampled length of stay is reached. What happened during the patient's stay in the hospital may or may not affect the sampled length of stay, depending on model assumptions.

Other Patient Attributes

Apart from the length of stay, other patient attributes that may potentially affect or be associated with transmission dynamics may include the vulnerability of the susceptible patient (e.g., age, sex) and the infectivity of the colonised patient (e.g., the number of colonised body sites).

Concurrent State Changes and Potential States

One of the identified advantages of ABS is its ability to handle multiple concurrent state changes of the agent (see Section 3.4.2). In HAI modelling, a patient agent may be simultaneously involved in one of the following streams of state changes:

- Colonisation status: depending on the nature of the pathogen under study, the colonisation status may include the states of susceptible, colonised but not

infectious, colonised and infectious, overt infection, immune to the pathogen and other possible colonisation states;

- Location status: depending on how detailed the layout of the hospital or hospital unit is represented in the model, different states may indicate which ward/bay/bed the patient stays.
- Detection status: potential states may include identified case (both negative and positive), unidentified case and case under investigation (i.e., sample is taken but result has not been reported);
- Decolonisation status: states may include under decolonisation treatment and not under decolonisation treatment; and
- Isolation status: potential states may consist of isolation in singe-bed isolation room, cohort isolation in side room or open bay, other types of isolation and not in isolation.

Behaviour Rules

Once the attributes and states of a patient agent are determined, the ABS model needs to define the rules that determine the initial attributes and states of a patient and, subsequently, how the patient changes state from one another. These rules may not only depend on the attributes and current states of the patient itself, but also the attributes and states of other patients (i.e., interaction between patients) and/or the current hospital setting (i.e., interaction with the hospital environment). For example, whether a patient may acquire colonisation or can be successfully isolated may depend on the attributes and states of both him/herself and other patient agents; while both successful detection of colonisation and isolation may depend on the hospital setting and policies.

When multiple concurrent state changes are modelled for a patient agent, it is possible that the state changes may be dependent on each other. For example, state change regarding detection status will clearly affect the state change of decolonisation and isolation status because normally only detected patients can be treated and isolated. These dependencies also need to be embedded in the behaviour rules.

In the context of modelling HAIs, the behaviour rules of patient agents are mainly reactive rather than proactive (see Section 3.6.1). The potential behaviour rules of patient agents may include:

- Colonisation development rules: the most important rule is how the susceptible patient acquires colonisation which will be discussed in detail in Section 3.7;
- Bed allocation and patient movement rules;
- Detection and screening rules; and
- Decolonisation treatment rules.

Ward Occupancy

In an ABS model, each individual patient agent may follow his/her own path of admission, discharge and movements governed by behaviour rules. Therefore, ward occupancy may vary and fall below 100% due to the model dynamics and bed availability. This is a more realistic representation of the actual situation and, further more, the model can be used to explore the potential impact of changed ward occupancy levels.

Apart from patient agents, other types of agents may be necessary for a model if they serve as vectors for the transmission of HAIs. These agents may include HCWs, visitors, and non-human objects (e.g., common toilets). Appendix A discusses how these types of agents can be represented in the ABS model.

3.7 Modelling Infection Transmission

Representing the transmission process of the infectious disease is the key of any epidemiological model. In theory, the transmission of a pathogen among patients in the hospital needs source of transmission (e.g., colonised patients), target of transmission (i.e., susceptible patients) and, in case of cross-transmission, vectors (e.g., HCWs and visitors). The potential transmission routes of HAIs include (1) transmission through direct patient-to-patient contacts; (2) cross-transmission between patients via transiently or permanently colonised HCWs or other human vectors (e.g., visitors); and (3) transmission from contaminated background environment (e.g.,

object surface). Different transmission routes may co-exist for the spread of a certain type of pathogen. Even with the advance of science, the existence and the relative importance of each transmission route for pathogens such as MRSA and *C. difficile* are not fully understood and quantified (Dziekan *et al.* 2000; Vos and Verbrugh 2005).

Depending on whether HCWs or any other vectors are explicitly represented, there are two classes of methods to model infection transmission: host-vector models (Bailey 1975) when vectors are explicitly represented, and mass action assumption (Anderson and May 1992) when only patients are considered. This section will discuss these methods with the focus on how they can be applied in ABS models. The pairwise action assumption, which is modified from the mass action assumption, is proposed to suit the ABS where individual characteristics need to be modelled.

3.7.1 Host-Vector Model

In the host-vector model, both hosts (i.e., patients) and vectors (e.g., HCWs) are explicitly represented. Conceptually, infection transmission occurs by first transmitting the pathogen from a colonised patient to a susceptible vector, and then from the colonised vector to another susceptible patient (Figure 3.4). Host-vector models are widely applied to HAI models (Austin and Anderson 1999; Cooper *et al.* 1999; Grundmann *et al.* 2004; Hotchkiss *et al.* 2005; Raboud *et al.* 2005; McBryde *et al.* 2007). Most previous applications divide patients and HCWs into several homogeneous compartments and model the transmission between patients and HCWs in an aggregate manner, while few represent them as individuals and explicitly model the physical one-to-one contacts (Hotchkiss *et al.* 2005).

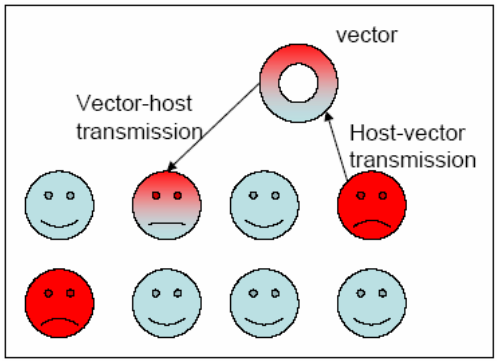

Figure 3.4 Infection transmission representation by host-vector model

A Host-vector model is conceptually a natural way to model infection transmission and fits the paradigm of ABS when patients and HCWs are individually represented. In ABS, the contacts between patients and HCWs can be explicitly modelled. The success of transmission through each contact is probabilistic in nature, which may depend on factors such as the nature of the contact (e.g., high risk or low risk contact) and the infectivity/vulnerability of patients/HCWs. The disadvantage of the approach is the large amount of data required to describe the contact structure and patterns between patients and HCWs, and the decolonisation rate of HCWs (e.g., from hand-washing) who are normally only transiently colonised. It is also difficult to estimate the baseline probability of successful transmission per contact. Another disadvantage is that when HCWs are explicitly represented, other potential important transmission routes (e.g., direct transmission between patients) may be ignored.

3.7.2 Mass Action Assumption

The mass action assumption has been widely applied in HAI modelling to represent infection transmission when HCWs are not explicitly represented (Cooper *et al.* 2004; Stone 2004; Robotham *et al.* 2006). Under the mass action assumption, patients and potential vectors (although not explicitly represented) are assumed to be homogenously mixed which means everyone interacts with equal probability with everyone else and possible heterogeneities arising from age, space or behavioural aspects are not included (Keeling and Rohani 2008). No explicit transmission route is assumed under the mass action assumption. Instead, transmission is assumed to be incurred by all possible transmission routes, including cross transmission via vectors. Figure 3.5 illustrates the mass action assumption. Mathematically, secondary cases (i.e., patients who acquire the infectious diseases during the hospital stay) occur at a rate proportional to the product of the number of colonised patients and susceptible patients.

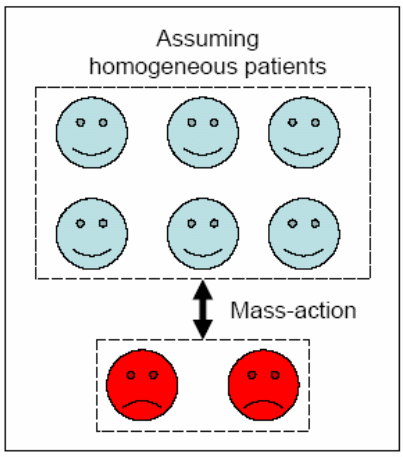

Figure 3.5 Infection transmission representation by mass action assumption

Mass action has two forms of expression depending on how we expect the contract structure to change with population size: the true mass action (or frequency dependent) or the pseudo mass action (or density dependent). If SP and IP represent the number of susceptible and colonised patients in the system, and C represents the constant transmission coefficient, then secondary transmissions will occur at a rate defined by $C \cdot IP \cdot SP/(IP + SP - 1)$ under true mass action and $C \cdot IP \cdot SP$ under pseudo mass action. True mass action principle assumes that the number of contacts is independent of the population size. In other words, each patient will have a fixed number of contacts (indirect with HCWs or direct with other patients) per time unit regardless how many patients are in the system. Therefore, as the number of patients in the system increases, the contacts of a patient will be distributed among a increasing number of patients and the chance that the patient may have direct or indirect contact with any specific patient will decrease. True mass action is thought to be more appropriate to model vector-borne pathogens and those with heterogeneous contact structure (Keeling and Rohani 2008) and is used by most previous HAI models. In this thesis, only true mass action is considered.

During a time step Δt , Equation 3.1 gives the number of new secondary transmissions during the time step.

$$T(\Delta t) = C \cdot \frac{IP \cdot SP}{IP + SP - 1} \cdot \Delta t \qquad (3.1)$$

where $T(\Delta t)$ is the number of new secondary transmission cases during time Δt which is measured in days,

C is the transmission coefficient which is defined as the number of secondary cases caused by one colonised patient per day, assuming a large population of susceptible patients,

IP is the number of colonised patients,

SP is the number of susceptible patients.

The basic reproduction ratio, or R_0, which is defined as "the average number of secondary cases caused by an infectious individual in a completely susceptible population" is widely used in epidemic theory (Anderson and May 1992). The parameter is normally directly used in community-based infection transmission models to quantify the transmission dynamics. For modelling HAI, which has a rapid turnover of patients (normally a few days), rather than directly applying R_0, the derived transmission coefficient or rate which represents "the average number of secondary cases caused by an infectious individual in a completely susceptible population per day" is normally used (Cooper *et al.* 2004; Bootsma *et al.* 2006). The transmission coefficient, or C, used in this thesis is in line with previous HAI models and has the same underlying assumptions of the basic reproduction number.

Given a fixed number of total patients (i.e., $IP+SP$) which means a constant denominator for Equation 3.1, increasing the number of colonised patients (i.e., IP) means a decreasing number of susceptible patients (i.e., SP). This indicates a non-linear relationship between the new secondary cases and the number of colonised patients. Given a constant C of 0.1 per day and total patient population of 30 (i.e., $IP+SP=30$), the non-linear relationship between $T(\Delta t)$ and IP under the true mass action assumption is illustrated in Figure 3.6. The figure shows that the number of new secondary cases reaches its peak when there are equal numbers of colonised and susceptible patients. The figure also demonstrates that, in a constant patient population, the depletion of susceptible patients (or the increase of colonised patients) will reduce the rate of new secondary cases.

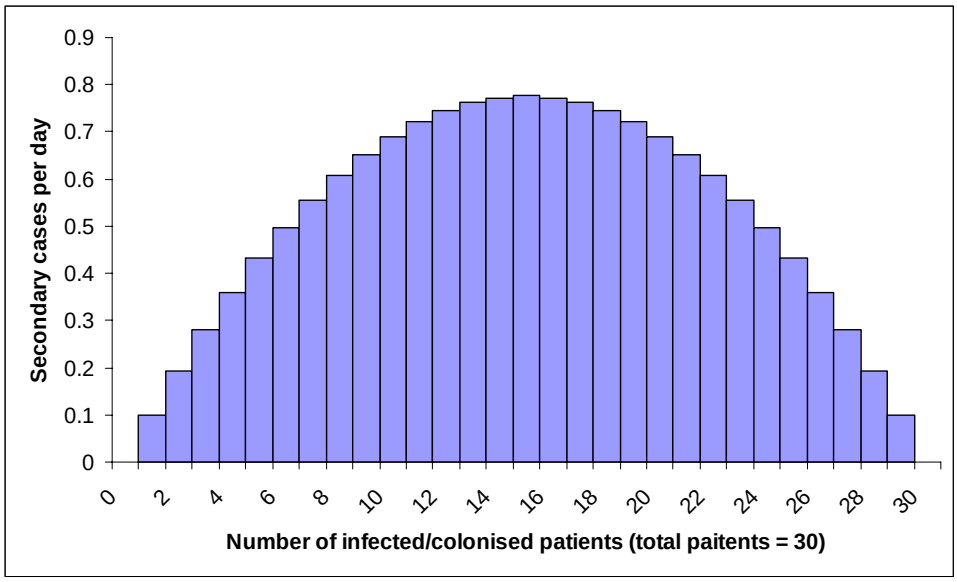

Figure 3.6 Non-linear relationship between the number of colonised patients and new secondary cases by mass action assumption

In order to fit into ABS model where patient agents need to be dealt with individually, Equation 3.1 needs to be modified so that the equation can represent the rate of colonisation of one susceptible patient during time Δt (see Equation 3.2). From an individual susceptible patient's point of view, given a fixed number of total patients, the risk of acquiring colonisation will increase linearly as the number of the colonised patients increases (Figure 3.7).

$$\lambda(\Delta t) = C \cdot \frac{IP}{IP + SP - 1} \cdot \Delta t \qquad (3.2)$$

where $\lambda(\Delta t)$ is the rate of colonisation of a susceptible patient due to the presence of colonised patients in the system during time Δt,

C, IP, SP share the same definitions as in Equation 3.1.

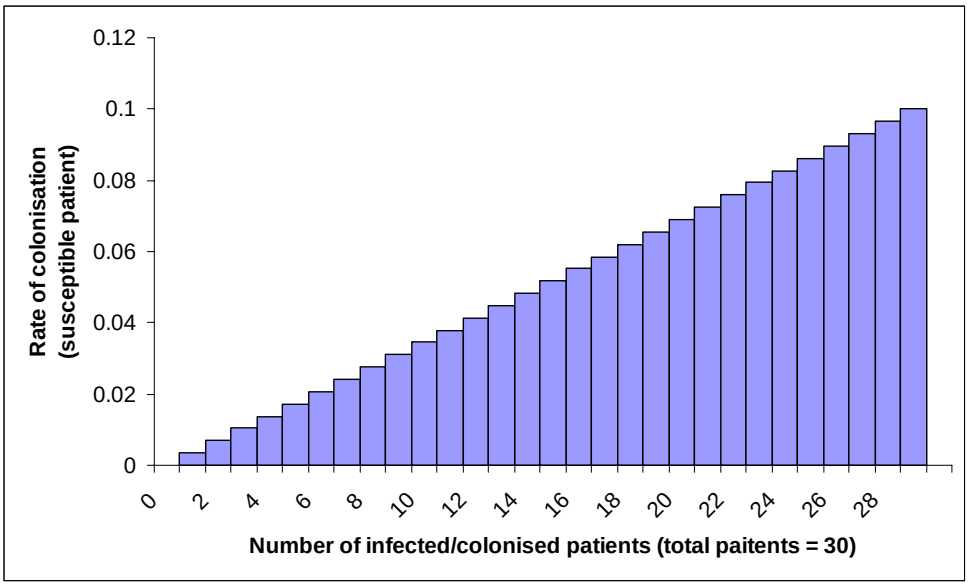

Figure 3.7 Relationship between the number of colonised patients and the rate of colonisation of a susceptible patient by mass action assumption

According to Equation 3.2, the rate of colonisation of the susceptible patient is bounded by the value of C (the rate equals to C when there is only one susceptible patient in the system while all other patients are colonised). Once the rate of colonisations is calculated, the transmission probability of the susceptible patient can be determined by Equation 3.3. Equation 3.3 is derived from the Poisson distribution, assuming the rate of events happening in the given period of time (i.e., Δt) is $\lambda(\Delta t)$. According to the probability density function of the Poisson distribution, the term $e^{-\lambda(\Delta t)}$ represents the probability that no event (i.e., the transmission of infectious diseases) happens during the time period; while $1-e^{-\lambda(\Delta t)}$ represents the probability that at least one event happens during the time period. Random numbers can then be applied to determine whether the event will actually occur.

$$P(\Delta t) = 1 - e^{-\lambda(\Delta t)} \quad (3.3)$$

where $P(\Delta t)$ is the probability that the susceptible patient get colonised due to the presence of colonised patients in the system during time Δt.

The mass action assumption can be directly applied to ABS models using Equations 3.2 and 3.3. The advantages of the mass action assumption include: no specific assumption about the potential transmission routes, less reliance on data, and mathematically sound and tractable. When observed data are limited, the approach may be the only option to model the infection transmission process. However the

standard mass action assumption also has many disadvantages. The main disadvantage is that it does not allow for individual characteristics (e.g., different vulnerability and infectivity) which may have a big impact on the infection transmission process. In order to overcome the problem, the mass action assumption will be modified to suit individual-based models such as ABS in the following section.

3.7.3 Pairwise Action Assumption

The pairwise action assumption, modified from the mass action assumption, aims to represent the infection transmission between pairs of patients considering the individual characteristics of each patient. Under the pairwise assumption, the probability of the transmission of the HAI of interest from a colonised patient to a susceptible patient is modelled between pairs of patient agents. Each patient is heterogeneous and has his/her own attributes which may affect the transmission probability. All possible pairs of susceptible-colonised patients are assessed separately and independently at each time step. The susceptible patient in the pair may have a specific vulnerability (e.g., age, ICU admission) while the colonised patient in the pair may have a particular infectivity (due, for example, to decolonisation treatment). Figure 3.8 illustrates the pairwise action assumption.

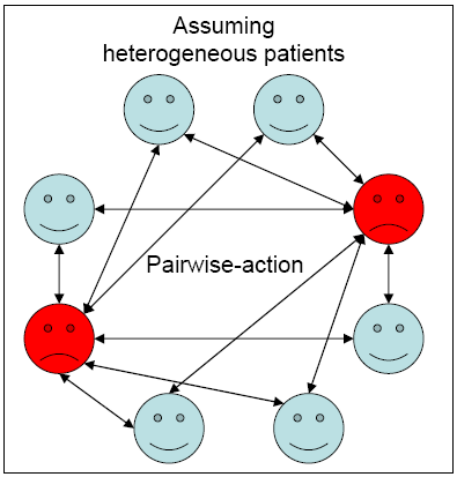

Figure 3.8 Infection transmission representation by pairwise action assumption

A mathematical expression of the rate of colonisations of the susceptible patient under the pairwise action assumption is given in Equation 3.4.

$$\lambda(\Delta t) = C \cdot \frac{V(v_1, v_2, \ldots) \cdot I(i_1, i_2, \ldots)}{n \quad -1} \cdot \Delta t \qquad (3.4)$$

where $\lambda(\Delta t)$ is the rate of colonisations of the susceptible patient in the pair may experience due to the colonised patient in the pair, during time Δt,

C is the transmission coefficient which is defined as the number of secondary cases caused by one colonised patient per day (with I=1), assuming a large population of susceptible patients with no additional vulnerabilities,

V is a function of different factors of $v_1, v_2, ...$ that may affect the vulnerability of the susceptible patient in the pair,

I is a function of different factors $i_1, i_2, ...$ that may affect the infectivity of the colonised patient in the pair, and

n is the total number of patients in the system.

Once the rate of colonisations of the susceptible patient is determined, Equation 3.3 can be applied to obtain the probability that the susceptible patient get colonised due to the colonised patient in the pair during time Δt. The pairwise action assumption retains the advantages of the mass action assumption while overcomes its disadvantage of assuming a homogeneous patient population.

Patient Location

In ABS, each patient agent may have states representing the specific ward/bay/bed location and corresponding behaviour rules governing the movements between locations (see Section 3.6.2). The representation of patient location in HAI models will make the model more realistic since it is expected that the spatial adjacency of two patients will affect the chance of contacts/interaction, and therefore transmission between them.

Under the pairwise action assumption, the relative spatial adjacency between the two patients in the pair can be incorporated into the transmission probability equation. How the patient locations affect transmission depends on the level of detail the patient locations are represented. If every bed location in the hospital or hospital unit is explicitly modelled, then the likelihood and intensity of interactions between the two patients may be represented as a function of the distance between the two patients. However, such an approach needs large amount of data and the model may not be generic to suit different hospital layouts and settings. Furthermore, the intensity of

interactions may not be a linear function of the distance between the two patients, since the layout of the hospital or hospital unit will also affect the degree of interaction among patients (e.g., two patients in two different wards or ward bays may have low level of interaction even distance between them is short).

An alternative approach to embed spatial location in the pairwise action assumption is to represent the ward and/or ward bay location in a hospital-level model, or to represent ward bay location in a hospital unit level model. This approach may need far fewer data. When two patients are evaluated by pairwise action assumption, the model can check whether the two patients stay in the same local environment (e.g., same ward bay) and incorporate this information into the transmission probability equation. It is expected that two patients in the same local environment have a higher level of interactions than two patients from different local environments. The rationale for treating global and local contacts differently when studying stochastic infection transmission is discussed in detail by Koopman *et al.* (2002).

An implementation of the pairwise action assumption which considers both patient infectivity/vulnerably and patient locations is demonstrated in the MRSA case study model in Chapter 4.

3.7.4 Choice of Methods

The choice of different methods for modelling infection transmission should be mainly determined by the nature of the infectious disease under study, the model assumptions made and the availability of the data. In theory, the three methods can all be applied in the ABS model. In fact, simple ABS models have been successfully built to implement both host-vector models and the standard mass action assumption based on two previous MRSA modelling studies (Cooper *et al*. 1999; Robotham *et al.* 2006) before ABS was applied to the MRSA case study (see Section 4.2.2 and Appendix B).

As a general guidance, the host-vector model may be adopted if the cross transmission route (facilitated by vectors) and its relative importance compared to other transmission routes are well understood; and data regarding contact structure and patterns, transmission probability per contact, decolonisation rate of HCWs are

readily available. Otherwise, the mass action or the pairwise action assumption may be applied to deal with models where vectors are not explicitly represented. Compared to the pairwise action assumption, the mass action assumption might be easier to implement since no additional information about the individual characteristics of the patients are needed. Pairwise action assumption is more realistic and flexible, and suits the needs of ABS since individual characteristics can be represented to estimate the transmission probability. Furthermore, the effect of spatial adjacency between pairs of patients can be modelled by pairwise action assumption.

3.7.5 Time Advance Mechanism

There are two main time advance mechanisms in the computer simulation, one is time-slicing and the other is event-driven (see Section 3.3.2). In theory, ABS can apply both types of time advance mechanisms.

When modelling infection transmission, there may be problems in applying the event-driven method. The event scheduling engine maintains a list of the next events of each patient in the simulation. If, for example, the next event for a patient is that the patient gets colonised then the newly colonised patient will pose an additional risk to all the remaining susceptible patients when the colonisation event happens. This will potentially affect the next event of every single susceptible patient in the system. The next events list will need to be reassessed.

In a HAI model, many events (e.g., admission/discharge of colonised patients, movements of colonised patients, isolation, decolonisation treatment) will affect the future events of every susceptible patient in the system regarding when they will acquire colonisation. Constantly updating the events of all susceptible patients is difficult. A further problem is that, even if it is possible to update the events of every susceptible patient frequently, it is difficult to quantify how the original scheduled colonisation event should be adjusted. Due to the potential problems of using event-driven time advance mechanism to model infection transmission, the time-slicing method may be a reasonable choice Under the time-slicing mechanism, possible secondary transmissions are evaluated during each time slice.

Regardless of what methods are applied to model infection transmission, the rate of colonisation of each susceptible patient during the time slice is calculated (e.g., using Equation 3.2 or 3.4) based on the system situation at the end of the time slice. Then, the rate of colonisation can be transformed to the transmission probability during the time slice using Equation 3.3. Finally, random numbers will be applied to determine whether the transmission actually occurs to each susceptible patient.

3.8 Experimental Factors and Model Responses

Experimental factors and model responses are two important elements of the model. Experimental factors are input parameters and structural assumptions composing the model; while model responses are output performance measures (Law 2007). From the perspective of modelling HAIs, experimental factors can be divided into two categories: those regarding intervention policies to prevent and control the transmission of HAIs and those regarding influencing factors that may potentially have a big impact on the transmission of HAIs. For intervention policies, people normally have certain degree of control and the focus is to evaluate the effectiveness and robustness of them. As to influencing factors, people normally have less control and the focus is the sensitivity analysis to measure their impacts on infection transmission.

3.8.1 Intervention Policies

A group of intervention policies which are widely implemented in practice and studied in theory are known as the "Search-and-Destroy" (S&D) strategy (see Section 1.2.3). Cooper *et al.* (2004) suggested that a policy of screening newly admitted patients for MRSA coupled with rapid and effective isolation and treatment may make a major contribution to controlling the spread of MRSA.

Screening Method

The first step of S&D strategy is the pre-emptive "searching" or screening of colonised patients. Infected patients normally have overt symptoms which make them easier to identify compared to colonised patients who do not have clinical identifiable symptoms but still are able to transmit the pathogen. Pre-emptive screening of

colonised patients is therefore the key to the success of S&D strategy. When alternative screening methods exist, the choice of which screening test to apply is an important decision that may affect the effectiveness of the overall S&D strategy.

All screening tests have some common features which describe the quality (e.g., sensitivity and specificity), cost and the speed (e.g., turnaround time) of the test. Sensitivity is the ability of a test to identify correctly individuals who have a given disease or condition; while specificity is the ability of a test to correctly exclude individuals who do not have a given disease or condition.

Turnaround time is an important feature of a screening test. In the narrow sense, turnaround time is the time required in the laboratory to obtain the test result from the sample. In the broad sense, it is the overall time between the sample is taken from the patient and the time the test result is reported. The turnaround time of a test in the narrow sense is the inherent nature of the test; while in the broad sense it is subject to many external uncertainties such as the way the hospital handles sample transportation and the delay caused by the communication of the results.

Shorter turnaround time should enhance the effectiveness of S&D strategy because the sooner the colonised patients are identified, the quicker follow up "destroy" policies can be applied to stop the transmission. For example, some previous studies demonstrated the effectiveness of the rapid PCR test (which reduces the test turnaround time from up to four days to a few hours) in reducing MRSA transmissions in the hospital setting (Harbarth *et al.* 2006; Cunningham *et al.* 2007; Hardy *et al.* 2007).

Screening Strategy

Once the screening method is chosen, a strategy is required to organise the screening tests. Many options are available as to the timing and frequency of the screening tests:

- Admission screening only (Harbarth *et al.* 2006; Cunningham *et al.* 2007);
- Random interval repeat screening (Robotham *et al.* 2006);
- Fixed interval repeat screening (McBryde *et al.* 2007);
- Admission coupled with random interval repeat screening;

- Admission coupled with fixed interval repeat screening (Cepeda *et al.* 2005; Pan *et al.* 2005; Hardy *et al*. 2007); and
- For research purpose, patients may also be screened on discharge (Hardy et al. 2007) or even after discharge (Fung et al. 2002).

Options available regarding the types of patients involved in the screening include:

- All patients (Hardy *et al.* 2007);
- Patients deemed as high-risk due to factors such as previous infection history, prior to surgical operations and transferred from areas where certain HAI is endemic (Pan *et al.* 2005).

Potential options of screening strategy include all possible combinations of the "timing and frequency of the test" and "the types of patients involved". Theoretically, the more frequent of the tests and the more patients involved, the better the chance to detect asymptomatic colonised patients.

Isolation

Once colonised patients are identified by screening tests, one "destroying" policy is to physically isolate these patients to minimise their contacts with susceptible patients. Pre-emptive isolation of all or high-risk patients on admission has also been implemented in practice (Harbarth *et al.* 2006). In reality, different types of isolation facilities exist and their effects on confining the colonised patients may vary. Single bed room with en-suite facility and air circulation system is the ideal option. However most single bed rooms in the UK hospital do not have these facilities. Side room or side bay with few beds are often used to isolate patients in practice. Cohort nursing (sometimes known as cohort isolation), which refers to grouping colonised patients together in a ward bay and assigning designated nurse(s), is also a form of isolation.

Identified colonised patients can only be isolated if an isolation facility is available at the time of request and if the patient is clinically appropriate to be isolated. The number of isolation facilities, ward occupancy and patient characteristics may all affect the chance of successful isolations.

The effectiveness of the isolation policy is quite controversial. Based on a 12-month study of a large UK teaching hospital where pre-emptive screening is not practised, Wigglesworth and Wilcox (2006) observed that of all the isolation needs due to infection control purpose, 22% may not be met within the first 24 hours. The percentage may be considerably higher if pre-emptive screening is practiced (since the isolation requests may increase). They concluded that insufficient capacity to isolate patients is common and may compromise infection control efforts.

Decolonisation

Apart from isolation, another key "destroy" policy is the decolonisation treatment. Decolonisation refers to the medical treatment to reduce or eradicate the pathogen from the colonised/infected patients. The treatment may last a few days and at the end of the treatment, a proportion of patients may recover and no longer pose a risk to other patients. During the treatment, the risk posed by the colonised patients (i.e., the infectivity of the patient) may be reduced.

Other Intervention Polices

Apart from the S&D strategy, other intervention policies have also been implemented in practice or proposed in theory to prevent and control HAIs. These interventions may include:

- Hand hygiene and general hygiene of the hospital unit (Forrester *et al.* 2005);
- Barrier precaution measures (Grundmann *et al*. 2002). For identified colonised patients, barrier precaution measures may be applied such as wearing disposable gloves and gowns, and stringent enforcement of hygiene rules;
- Ward closure (i.e., stop admitting new patients) which is sometimes implemented in practice (Barrett *et al.* 1998). If ward closure is modelled, the conditions to close and reopen the ward need to be specified; and
- Screening HCWs and treatment of colonised HCWs (Fitzpatrick *et al.* 2000). If S&D strategy also applies to HCWs, the identified colonised HCW may be temporarily excluded from the job until he/she recovers.

3.8.2 Influencing Factors

Endemic Setting

Endemic setting refers to the proportion of patients who have already been colonised with the HAI of interest on admission. These patients are known as primary cases and will pose a risk to susceptible patients as soon as they are admitted to the hospital. In the long term, there is a feedback relationship between eradicating the pathogen within the hospital and the lower community prevalence which should then be reflected by a smaller proportion of primary cases back in the hospital. However, in the short term, the hospital has little control over the endemic setting.

Length of Stay

The patient's length of stay has a big impact on the transmission dynamics of HAIs (see detailed discussion in Section 3.6.2). The hospital may reduce the average length of stay in the long term, probably by changing hospital guidelines or introducing advanced health technologies. However, length of stay is normally not controllable in the short term.

Transmissibility

Transmissibility is mainly the inherent nature of the specific (strain of) infectious disease under study. It describes the average ability of the pathogen to transmit among patients. In HAI modelling, when vectors (e.g., HCWs) are not represented, transmissibility is normally defined as the average number of secondary cases incurred in a time unit (e.g., one day) by one primary case assuming a large number of susceptible patients. When vectors are explicitly modelled, transmissibility may be defined as the probability of transmitting the pathogen between a patient and a vector per contact. Intervention policies and other influencing factors may affect the transmission dynamics, but they should not affect the underlying transmissibility.

Effectiveness of Intervention Policies

Although the hospital may have control over intervention policies, it normally has less control over how effective the intervention policies are. The influencing factors which concern the effectiveness of intervention policies include (1) the effectiveness of isolation; (2) the effectiveness of decolonisation on reducing the infectivity of colonised patients during their treatment; (3) the effectiveness of improved hygiene

(both hand hygiene and environment hygiene); and (4) the effectiveness of barrier precaution measures.

3.8.3 Model Responses

Model responses are the model outputs which are used to monitor the transmission situation of the hospital, or served as performance measurements of the intervention policies.

Number of Secondary Cases

Secondary cases, also known as nosocomial cases, are patients who do not have the HAI of interest on admission but later acquire colonisation during the hospital stay. Although the hospital has less control over the number of primary cases, it can intervene to minimize the number of secondary cases.

The number of secondary cases is naturally correlated with the number of primary cases which are the source of transmission in the first place. Therefore, when performing comparison studies, the number of secondary cases is only a good model response if both scenarios have similar level of primary cases; otherwise, the model response may be misleading. For example, if the first scenario which adopts intervention A has 20 primary cases and 40 secondary cases; the second scenario which adopts intervention B has 100 primary cases and 50 secondary cases; and all other conditions are similar between the two scenarios. Although the first scenario has fewer secondary cases, it is misleading to conclude that intervention A (where 20 primary cases lead to 40 secondary cases) is more effective than intervention B (where 100 primary cases only lead to 50 secondary cases).

Transmission Ratio

The transmission ratio is the number of secondary cases divided by the number of primary cases in the same period. The transmission ratio considers both primary and secondary cases and thus may be a fair and reasonable model response to compare different scenarios with different levels of primary cases. Using the same example in the previous section, the transmission ratios are 2 (2 = 40 / 20) and 0.5 (0.5 = 50 / 100) respectively for the two scenarios. It is clear that intervention B appears to be more effective than intervention A.

It may be misleading to simply report the transmission ratio without specifying the levels of primary and secondary cases. For example, two scenarios with same number of total admissions may have the same transmission ratio of 0.5 over the same period of time, while the numbers of primary and secondary cases are 50/100 and 20/40 respectively. If only the transmission ratios are reported, the fact that the first scenario has a worse overall infection situation will be hidden. It is also helpful to report the corresponding total admissions to give a rounded picture of the transmission situation.

Prevalence

Prevalence refers to the proportion of colonised patients (both primary and secondary cases) in the hospital at a given time. Prevalence is appropriate to assess the overall infection situation. It is, however, less satisfactory to measure the effectiveness of intervention policies since it does not consider the relative ratio between primary and secondary cases.

Other Model Responses

Other model responses which have been used to measure the transmission dynamics of HAIs include:

- Colonisation/infection patient-days which reports the accumulated number of days colonised patients stay in the hospital (Cooper *et al.* 1999);
- Isolation patient-days which represent the accumulated number of days isolated patients stay in the hospital (Bootsma *et al.* 2006); and
- Attack rate which is defined as the rate at which a susceptible patient get colonised (McBryde et al. 2007).

3.9 Experimental Design

Experimental design is about systematically setting the level of various experimental factors to see the impact on model responses, and it should be an integral part of the whole simulation project (Kleijnen *et al.* 2005). For the study of HAIs, experimental design provides the tool to systematically evaluate the effectiveness and robustness of various intervention policies and test the sensitivity of various influencing factors.

The main experimental design methods that have been applied in the thesis are fractional factorial design and response surface design. Justification of using these methods and their detailed descriptions are given in Section 6.2.

3.10 Summary

Based on previous chapters, the overall research objectives and questions of the thesis were derived at the beginning of the chapter. The following sections of the chapter aim to address the main methodological issues of these research questions.

A taxonomy of potential methods for modelling HAIs was proposed and the relative advantages of ABS compared to cohort/aggregate models (e.g., Markov models, SD) and other types of individual-based models (e.g., DES) were identified using the proposed taxonomy. These analyses have helped to justify the usefulness and potential benefits of applying ABS to the modelling and management of HAIs.

Two key aspects of modelling HAIs using ABS are the representation of patient agents and the modelling of the infection transmission process. The representation of patient agents by attributes, states and behaviour rules were described. Key features of patient agents (compared to previous models), such as non-exponentially distributed length of stay, multiple concurrent state changes and changing ward occupancy were discussed in detail. Different methods for modelling infection transmission were introduced with a focus on the mass action assumption, where vectors (e.g., HCWs) are not explicitly modelled. In order to suit the needs of individual-based models such as ABS, the pairwise action assumption was proposed, modifying the mass action assumption. The key features of the pairwise action assumption were discussed including how individual vulnerability/infectivity and how spatial locations can be incorporated. The problem of using event-driven time advance mechanism to model infection transmission was discussed and the time-slicing method was proposed to be the alternative approach.

To address the last research question of the evaluation of various MRSA intervention polices, the potential experimental factors and model responses, and the types of chosen experimental design methods were described. In general, this chapter has justified and addressed the main methodological issues of modelling HAIs using ABS.

Chapter 4

Agent-based Simulation Model of MRSA

4.1 Introduction

In order to test the methodology and the modelling framework described in Chapter 3 on a specific HAI, an agent-based simulation model of MRSA is proposed in this chapter. Based on an empirical study in a UK hospital, the MRSA model will also be used to evaluate the effectiveness of various interventions. In this chapter, the background of the research study is introduced and the key features of the model are described. Then, two key aspects of the model, patient behaviour rules and the modelling of infection transmission, are discussed. Finally, the hierarchical model structure which consists of the overall system environment (i.e., the hospital ward) and the local patient agents are presented.

4.2 Project Background

4.2.1 Background

The building of a simulation model was originally part of a research study (Hardy *et al.* 2007), funded by the Department of Health in the UK, to test whether screening MRSA using a rapid PCR test, which may provide results within a day, is more effective and cost-effective than the established culture test which may take up to four days to obtain results. The main research study was designed as a prospective randomised two-period cross-over study at Birmingham Heartlands Hospital, a typical large general teaching hospital in the UK which has more than 1,000 beds. The project involved seven surgical wards (denoted as ward A, B, C, D, E, F and G hereafter) and lasted for sixteen months. In the first eight months, four hospital wards (i.e., wards A, B, C and D) adopted the PCR test while the other three wards (i.e., wards E, F and G) continued to use the conventional culture test. After eight months,

there was a cross-over with the first four wards adopting the culture test and the other three the PCR test. Overall, fourteen scenarios were generated from the study with each ward being associated with two scenarios, one for the culture test period and the other for the PCR test period. In order to concentrate the sole effect of the rapid screening test, all controllable factors and intervention measures were kept the same between the culture and PCR test period for each study ward except the choice of screening test itself.

Apart from general infection prevention and control measures such as hand-washing, staff education and standard barrier precaution measures, active S&D strategies, including pre-emptive admission and repeat screening test, isolation and decolonisation treatment, were also implemented across all study wards. Detailed information regarding MRSA colonisation status, screening test, isolation, decolonisation treatment, ward movement, operation history, antibiotic treatment, demographics and other potential risk factors were collected for each patient. Observed data were kept in both an Access database and Excel spreadsheets. During the sixteen-month study period, 12,732 patients were admitted to the seven study wards with a total of 13,952 ward admission/re-admission episodes (a patient may be admitted to the ward several times). Altogether, 30,490 screening test samples were taken with 12,682 being admission screening tests and 17808 being repeat screening tests. Overall, 453 patients were identified as colonised with MRSA by admission screening tests (i.e., primary cases) and 268 patients were identified to have acquired MRSA colonisation while they stayed in the hospital by repeat screening tests (i.e., secondary cases).

Statistical analysis of the research study has demonstrated the effectiveness of the rapid screening test in reducing MRSA transmission in the hospital setting. Compared to study periods when culture screening tests were adopted, the transmission ratio, which is the ratio of the number of secondary cases to the number of primary cases, was significantly reduced in six out of seven study wards when rapid PCR screening tests were applied (Hardy *et al.* 2009).

Compared to statistical analysis, ABS model can describe the transmission dynamics of MRSA over time and evaluate the theoretical mean effectiveness of the rapid

screening test when randomness is considered. Furthermore, the model can systematically explore scenarios that have not been implemented in the research study, such as the evaluation of other intervention policies (e.g., screening strategy, isolation and decolonisation treatment), and the sensitivity analysis of influencing factors (e.g., patients' lengths of say, transmissibility of MRSA and the proportion of patients colonised with MRSA on admission).

4.2.2 Test Agent-based Simulation Model on Previous Studies

Before the full-scale ABS model was built, two preliminary tests were performed to use an ABS model to replicate the assumptions and results of two previous MRSA studies adopting mathematical compartmental models. The first study (Cooper *et al.* 1999), which focused on a single hospital unit, explicitly considered both patients and HCWs and classified them as either susceptible or colonised. The model assumed that the only transmission route of MRSA is patient-to-patient cross transmission via transiently colonised HCWs. Other main assumptions of the model include constant patient population, 100% bed occupancy, fixed detection rate, immediate removal of detected colonised patients and 100% hand-washing efficacy. An ABS model was built in Anylogic® to replicate the assumptions of the model. Applying the model, the same model experimentations were performed with the same input parameter values of the original model. In all scenarios tested, which include changing the transmissibility, changing the probability of colonisation on admission and changing the detection rate, the results of the ABS model closely matched that of the original mathematical model.

The second study (Robotham *et al.* 2006), which represented the whole hospital and its community, only considered patients and divided them into eight different compartments that included susceptible patients, undetected colonised patients, detected colonised patients who are isolated, detected colonised patients who are not isolated and other four compartments representing people in the community with different MRSA colonisation status (susceptible or colonised) and readmission rate (high or low). The model did not assume any explicit MRSA transmission route and infection transmission was assumed to follow the mass action assumption. Other assumptions of the model include fixed patients and community population, transmission only occurs in the hospital, isolation can perfectly prevent transmission

and colonised patients can be decolonised with a natural recovery rate. An ABS model was built in Anylogic® to replicate the assumptions of the model. Due to the large community population size (around 170,000 people), only patients in the hospital (1000 patients) were represented individually as agents while the different groups of people in the community were represented as integer variables. The ABS model and the original model were compared with the same input parameter values. In all the scenarios tested, the results of the ABS model closely matched that of the mathematical model.

The main purpose of the two pilot models was to demonstrate that ABS can be at least as good as existing mathematical compartmental models to describe and study MRSA transmission dynamics even without further exploring the distinctive features and the identified relative advantages of ABS. Another aim was to test and get familiar with the software, Anylogic®, before it was used to develop the full-scaled MRSA model. Appendix B gives a detailed description of the two test ABS models and the comparisons with the mathematical models.

4.3 Model Features

The proposed model has the following key features which both comply with the general requirements of ABS and take into account of the specific characteristics and data availability of the MRSA research study.

4.3.1 Model Objectives

From the perspective of the MRSA study, the model objectives are to apply ABS to describe the transmission dynamics of MRSA in the hospital setting, to evaluate the effectiveness of various intervention policies to prevent and control MRSA (including single effectiveness and potential interactions among different factors), to test the sensitivity of various influencing factors that potentially affect MRSA transmission, and eventually to indicate the best practices to manage MRSA in the hospital setting. From the perspective of exploring ABS methodology and application, the objectives of the modelling study are to demonstrate that, compared to other modelling methods, ABS has many advantages and it is an effective, robust and flexible technique to

model the transmission dynamics of HAIs such as MRSA, and to show the feasibility of the modelling framework proposed in Chapter 3.

4.3.2 Model Setting

The scope of the model is a single hospital ward divided into bays, with some isolation rooms. It is assumed that most MRSA colonisation will be transmitted within a ward, rather than amongst the wider hospital or community population.

The only type of agent represented by the model is the patient. HCWs do get colonised and are an important vector in the transmission of MRSA and some previous models represented them explicitly. In this model, they are represented implicitly by the pairwise action assumption which is modified from the mass action assumption (see Section 3.7.3).

4.3.3 Ward Representation

Each ward bay may have up to six beds; while each isolation room has only one isolation bed. Ward bays and isolation rooms are explicitly modelled but the location of patients within the bays and the location of the bays within the wards are not. The admission, discharge and movement of each patient are governed dynamically by the relevant behaviour rules of the patient (see Section 4.4). Consequently, throughout the simulation, the number of patients in the ward is not constant but determined by the model dynamics and bed availability.

4.3.4 Patient Representation

Each patient agent is created when admitted to the ward and disposed of from the model when discharged from the ward. Apart from the behaviour rules, each patient agent has distinctive attributes and states. It is the combination of attributes, states and behaviour rules that define the patient in the model.

The attributes that are represented in the model include the length of stay of the patient and indications of the patient's vulnerability to infection including whether the patient has been admitted to ICU during the hospital stay and whether the patient has been fitted with invasive devices during the ward stay (e.g., an intravenous catheter).

These attributes are widely recognised as having a significant impact on the transmission dynamics of MRSA (Bootsma *et al.* 2006; Noah 2006).

ABS can efficiently handle multiple concurrent state changes of a patient agent (see Section 3.6.2). In this model, the states of a patient agent can be theoretically grouped into one of the following categories:

- Colonisation status which includes two states: susceptible and colonised;
- Detection which contains three states: undetected, screened but waiting for the result and detected;
- Decolonisation treatment which has two states: under decolonisation treatment and not under decolonisation treatment; and
- Location which comprises the states that represent the possible locations a patient can be situated in the ward including the different bays and isolation beds.

At any time during the ward stay, a patient must be in one and only one state in each category. For example, a patient agent may currently be colonised with MRSA (colonisation status), has been screened but is waiting for the result (detection), has not received decolonisation treatment (decolonisation treatment) and is situated in a bed in a specific ward bay (location). The patient will change state according to the behaviour rules described in Section 4.4.

4.3.5 Transmission of MRSA

The transmission of MRSA between patients in the ward is modelled by pairwise action assumption, which takes into account individual patient characteristics (see Section 4.5 for detailed discussion).

4.3.6 Intervention Policies and Influencing Factors

The prevention and control policies embedded in the model include pre-emptive admission and repeat screening tests, rapid screening tests, isolation of detected colonised patients and decolonisation treatment for detected colonised patients. These intervention policies were also implemented in the research study and therefore observed data are available to reflect the actual characteristics of the interventions

(e.g., the actual turnaround time of PCR and culture tests, and the duration and success rate of the decolonisation treatment).

The model also incorporates many influencing factors which potentially may have a big impact on MRSA transmission. These factors include MRSA endemic setting (the proportion of patients colonised with MRSA on admission), patients' lengths of stay, the transmissibility of MRSA, the effectiveness of decolonisation treatment and the proportion of transmission coming from within the same bay compared to the whole ward.

4.3.7 Model Responses

The main model responses, or model outputs, are the number of patients who are MRSA negative on admission (i.e., primary cases), who become colonised during their ward stay (i.e., secondary case) and the corresponding transmission ratio which is the ratio of secondary cases to primary cases. The first measurement reflects the absolute number of secondary cases during the study period while the second response indicates the relative extent of MRSA transmission allowing for both the numerator and denominator. As the hospital can not generally control the proportion of primary cases admitted, the transmission ratio is a more objective output to measure the effectiveness of hospital interventions, especially in the short term.

For model validation purpose, apart from the two main model responses, the time to detection, i.e., the delay between the time a patient is admitted to the time MRSA colonisation is detected, is also used as a model response to be compared with the corresponding observations.

4.3.8 Time Advance Mechanism

The two time advance mechanisms and their use in modelling infection transmission were discussed in Section 3.7.5. Both mechanisms are applied in this model. The time-slicing approach is used to model the transmission of MRSA; while the event-driven approach is applied to schedule the rest of the activities and events (e.g., screening tests for patients, patients discharged from the ward and patient movements within the ward) generated by the model. It is not unusual to apply both time-slicing

and event-driven time advance mechanisms in the same simulation model. In fact, the time-slicing can be deemed as special events which happen in fixed time intervals.

4.3.9 Simulation Package and Random Number Generator

The model was built in Anylogic®, one of the few commercially available simulation packages that support the development of ABS. Like any ABS package other than general computer languages such as Java and C++, it is relatively quick to design and build the model structure in Anylogic®. Standard techniques of ABS, such as message exchange mechanism and agents' space awareness and movement functionality, are supported by the package. Complex states and behaviour rules of the agent can be developed by a special model construct, called the state-chart. In a state-chart, the states of an agent can be defined together with the rules of how the agent changes from one state to another. Simple rules can be set by built-in functions while sophisticated rules can be designed by Java scripts. Apart from ABS, Anylogic® also supports DES and system dynamics, making it easier to handle both time-slicing and event-scheduling time advance mechanisms at the same time.

The model did not use the standard random number generator of Anylogic® which is, in fact, the standard Java random number generator that is under criticism by many experts (L'Ecuyer 2001). Instead, the Mersenne-Twister random number generator (Matsumoto and Nishimura 1998), which is recommended and applied by many studies (Law 2007), is used for the model. Figure 4.1 illustrates the main features of the proposed ABS model.

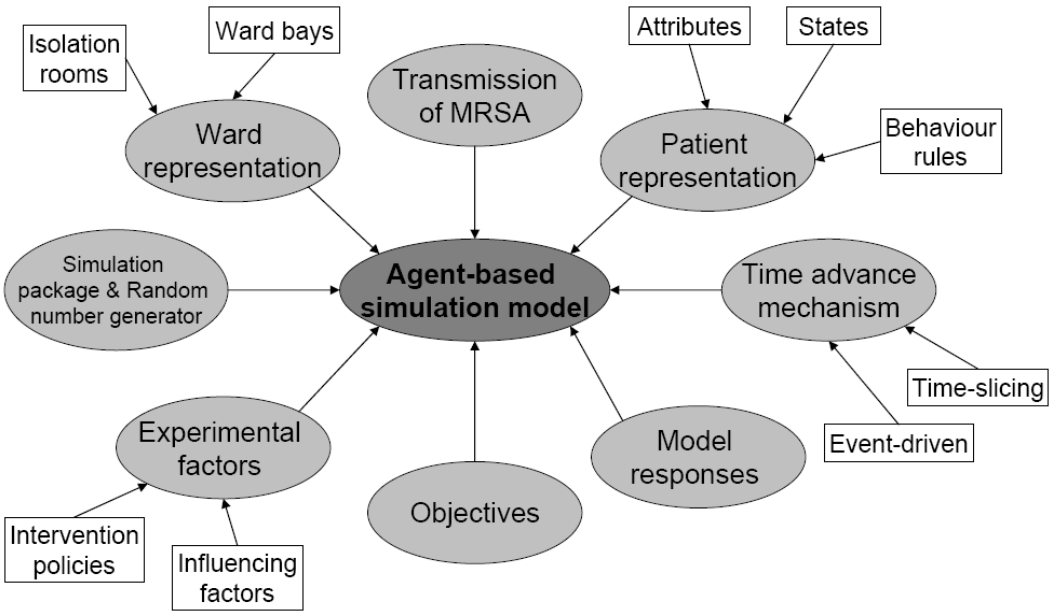

Figure 4.1 Main features of the agent-based simulation model

4.4 Patient Behaviour Rules

The fundamental feature of ABS is that the overall dynamics emerge or are driven by the behaviours of the locally defined agents. The rules described in this section will govern the behaviours of each patient agent and its interactions with other patient agents and with the ward environment.

4.4.1 Patient Admission and Discharge

Patient interarrival times are sampled from a globally defined interarrival distribution and, on arrival, the patient agent joins an artificial queue from which it is admitted to the ward when there is at least one empty bed (excluding isolation beds). If more than one bed is available, the patient will be randomly allocated to one of them. On admission, the patient has a certain probability of being already colonised with MRSA (i.e., primary case) or not (i.e., susceptible patient). However, the patient's MRSA status is unknown to the ward until the patient is screened and the test result is ready. The vulnerability of the patient is also determined at admission by sampling whether the patient has been or will be admitted to ICU and whether the patient will need an invasive device during the ward stay.

Two separate and independent distributions are used to sample patients' lengths of stay, depending on the patient's MRSA status on admission. The patient will be discharged from the ward when the sampled length of stay is met regardless of his/her other states in the model.

4.4.2 Detection by Admission Screening (Primary Case)

If admission screening is operational, each patient will have the MRSA screening test within two days of the admission. Assuming 100% test sensitivity and specificity then the MRSA status will be detected following a screening delay (the time taken for the pathology test and the communication of the results). If a patient has a positive result then intervention policies may be applied (see Section 4.3.6). During the screening delay, no interventions are introduced and the patient may transmit the MRSA pathogen to other susceptible patients. If the sampled length of stay is short, it is possible that the patient has already been discharged by the time the screening result is reported.

4.4.3 Acquiring Colonisation

For a susceptible patient, the screening test, either admission or repeat screening, will simply confirm the negative status with no following intervention policies implemented. The most important issue for a susceptible patient is that he/she may become colonised during the ward stay (i.e., secondary transmission). The modelling of the transmission of MRSA is discussed in detail in Section 4.5.

4.4.4 Detection by Repeat Screening (Secondary Case)

When a susceptible patient becomes colonised with MRSA, the positive MRSA status will not be detected immediately and the patient will start to pose a risk to other susceptible patients. The colonisation of previously susceptible patients will only be detected if there is a policy of repeat screening and the results from that screening arrive before the patient is discharged. If the colonisation is detected, the patient may be isolated and/or receive decolonisation treatment.

4.4.5 Decolonisation Treatment

Decolonisation treatment will last for a few days and at the end of the treatment, the patient will be tested, maybe several times, to see if MRSA has been successfully

cleared. A patient who is deemed to be successfully decolonised is assumed to have returned to a susceptible state. A patient occupying an isolation bed following successful decolonisation will be transferred to a ward bay if there is a spare bed available; otherwise the patient continues to stay in the isolation bed. If the decolonisation fails, the patient will go through the treatment again. A colonised patient receiving decolonisation treatment is assumed to have a lower infectivity than an undetected colonised patient. Figure 4.2 illustrates the colonisation status, detection and decolonisation states of a patient and the main state transitions.

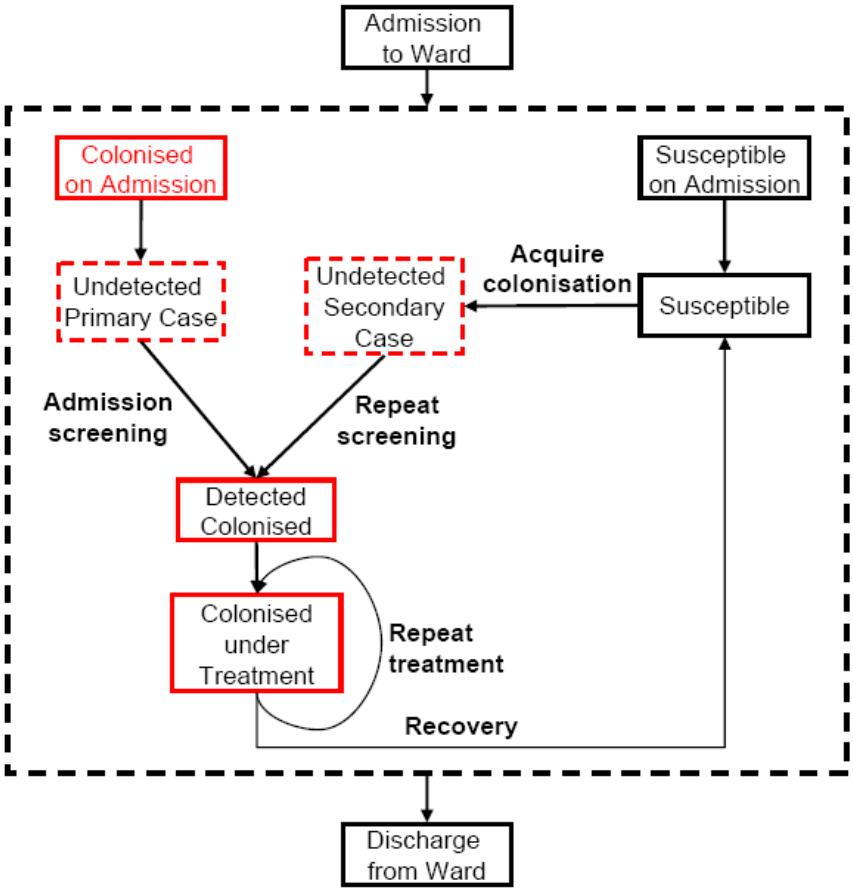

Figure 4.2 Patient colonisation status, detection and decolonisation states and main state transitions

4.4.6 Patient Location and Movements (including Isolation)

After admission, a patient may be moved from one bay to another. Furthermore, detected colonised patients will move to an isolation bed if there is one available. Not all isolation beds are used for the sole purpose of isolating MRSA colonised patients. The isolation beds may be used for patients with other types of infectious diseases (e.g., *C. difficile*) or patients with special clinical needs. Therefore, the model has a

parameter representing the probability that an isolation attempt fails due to a reason other than all isolation beds are occupied by MRSA colonised patients. As a result, isolation may fail even when the model suggests that there are empty isolation beds in the isolation rooms. Under such circumstances, to reflect the real ward situation, a random patient in the bay rather than the colonised patient will move to an isolation bed.

A patient who stays in an isolation bed will normally remain in isolation until the patient is discharged; the only exception is that if the decolonisation treatment is found to have been successful then the patient may move out. Figure 4.3 illustrates a patient's ward locations and movements in a hospital ward with three ward bays and one isolation room.

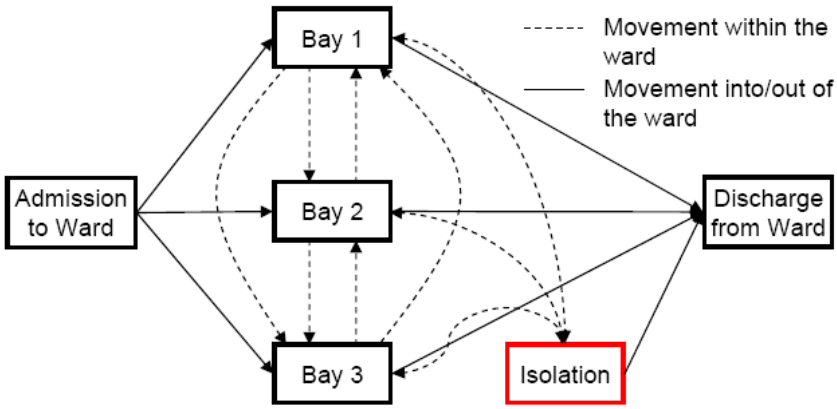

Figure 4.3 Patient ward locations and movements in the hospital ward

4.4.7 Type of Patient Agent

In the MRSA model, the behaviour rules of patient agents are normally reactive rather than proactive in nature. In other words, patient agents are largely controlled by the hospital and their behaviours are highly confined by the hospital environment. As a result, patient agents in the model are not as intelligent and adaptive as the agents in some ABS models. Among different definitions and categorisations of ABS and agents, the patient agents in the model fit in with North and Macal's concept of agents (North and Macal 2007). In their definition, agent potentially may have five different properties (see detailed description in Section 1.3.3) and agents may have some but not all of these properties. The important thing to be deemed as ABS is that the model is structured in such a way that missing features can be easily added within the established modelling framework. In the proposed model, patient agents are self-

contained independent individuals that are situated in the hospital environment and interact with other agents and the environment. They are not adaptive or proactive, but they are still agents who have complex reactive behaviour rules.

4.5 Model MRSA Transmission

The transmission of MRSA is modelled between pairs of agents, modifying the widely used mass action assumption (see Section 3.7.3). The general equations for determining the rate of colonisations of a susceptible patient and the transmission probability are given in Equation 3.4 and 3.3 in Chapter 3.

4.5.1 Transmission Probability Equations

In the ABS model, each patient is heterogeneous and has his/her own attributes which may affect the probability of transmission. All possible pairs of susceptible-colonised patients are assessed at each time step. The susceptible patient in the pair may have a specific vulnerability while the colonised patient in the pair may have a particular infectivity. The relative spatial adjacency of the two patients in the pair may also affect transmission.

Detected colonised patient

The infectivity of a colonised patient will be reduced if the MRSA colonisation is detected and he/she receives decolonisation treatment. The reduced infectivity is denoted by the parameter k, which is a multiplying factor and takes the value between zero (i.e., detection and treatment can totally eliminate the infectivity of the colonised patient) and one (i.e., detection and treatment have no effect in reducing infectivity during the treatment). When k takes a value in between, it means that the infectivity of the colonised patient is reduced by $(1-k)*100$ percent due to the detection and the decolonisation treatment.

Local versus whole ward interactions

The transmission probability equations also allow for the spatial adjacency of the two patients in the pair and treat the global and local interactions differently by introducing the parameter m. Each patient in the ward has two levels of interactions at the same time; one is the local interactions with adjacent patients within the same

ward bay (e.g., direct physical contacts between neighbouring patients), and the other is the global interactions with every patient in the ward, including the patients in the same ward bay and the isolation room (e.g., indirect contacts facilitated by the nurses or doctors who serve all patients in the ward). The parameter *m*, which takes the value from zero to one, represents the fraction of a patient's local interactions, while *(1-m)* represents the proportion of a patient's global interactions. Therefore, when two patients do not stay in the same bay, they can only have global interactions; while if the two patients stay in the same local environment, they will have both local and global interactions.

When both patients in the pair stay in the same bay, the multiplying factor of $\left(\frac{m}{n_{bay}-1}+\frac{1-m}{n_{ward}-1}\right)$ is included in the equation where the first term represents the transmission risk caused by local interactions and the second term represents the transmission risk caused by global interactions between the two patients. The parameters of n_{bay} and n_{ward} represent the total number of patients in the bay where the two patients in the pair stay and the total number of patients in the whole ward respectively. Alternatively, if two patients in the pair do not stay in the same bay, the multiplying factor of $\frac{1-m}{n_{ward}-1}$ is included in the equation which only reflects the global interactions.

Patient Vulnerability

The parameter V is a multiplying factor that represents the vulnerability of the susceptible patient in the pair where the 'normal' patient has the vulnerability of one. Therefore, the value of V may be above one if the patient has been admitted to ICU and/or needs invasive devices. Table 4.1 shows the equations for calculating the rate of colonisations the susceptible patient may experience due to the colonised patient in the pair during a single time step.

Table 4.1 Equations for calculating the rate of colonisations of susceptible patients

Scenarios	Colonised patient	Susceptible patient	Rate of colonisations
1	Undetected	Same bay	$\lambda(\Delta t) = C \cdot V \cdot \left(\frac{m}{n_{bay} - 1} + \frac{1-m}{n_{ward} - 1} \right) \cdot \Delta t$
2	Undetected	Other bays/Isolation	$\lambda(\Delta t) = C \cdot V \cdot \frac{1-m}{n_{ward} - 1} \cdot \Delta t$
3	Detected & Under Treatment	Same bay	$\lambda(\Delta t) = C \cdot V \cdot k \cdot \left(\frac{m}{n_{bay} - 1} + \frac{1-m}{n_{ward} - 1} \right) \cdot \Delta t$
4	Detected & Under Treatment	Other bays/Isolation	$\lambda(\Delta t) = C \cdot V \cdot k \cdot \frac{1-m}{n_{ward} - 1} \cdot \Delta t$

In the equations, the parameter *C* is defined as the number of secondary cases incurred by one colonised patient per day, assuming a large population of susceptible patients. In previous studies, the range of values of *C* was found to lie between 0.017 and 0.465 (Cooper *et al.* 2004; Raboud *et al.* 2005; Robotham *et al.* 2006; McBryde *et al.* 2007). The value of *C* may depend on the particular hospital environment and the patients involved in the study and will need to be re-assessed for each study. The value of *V* depends on the patient's risk factors and can be estimated from the relative risk or odds ratio (Stewart 2002). The parameter of *k* and *m* all take values between zero and one, and in the hospital setting where the average length of stay of patients is only a few days, the choice of time-slice, or Δt, is normally one day or even shorter. For the denominators, for a typical hospital ward where ward occupancy is normally above 80%, n_{bay} may take values up to six for a ward bay and n_{ward} may take values up to thirty or even more.

Once the rate of colonisations of the susceptible patient is obtained, the probability that the susceptible patient may actually get colonised can be calculated using Equation 3.3 (i.e., $P(\Delta t) = 1 - e^{-\lambda(\Delta t)}$).

4.5.2 Modelling Infection Transmission by Time-slicing

The time-slicing time advance mechanism is used to model MRSA transmission between pairs of patient agents. The interval between two successive evaluations is set at Δt days. At the end of each time-slice, all possible colonised-susceptible pairs are formed and evaluated separately and independently. Mathematically, if *Nc* and *Ns*

represent the number of colonised and susceptible patients in the ward at the end of a certain time-slice, then each colonised patient will form *Ns* pairs, each susceptible patient will form *Nc* pairs, and thus the total number of pairs formed and evaluated during the time-slice is *NcNs*. This implies that a single susceptible patient will be evaluated multiple times during one time-slice if there is more than one colonised patient in the ward. Under such circumstances, since each pair evaluation is independent and separate, the susceptible patient will become colonised as long as one of the evaluations determines a transmission actually takes place.

4.6 Model Structure

The MRSA model has a hierarchical structure which consists of the overall system environment, i.e., the hospital ward, and the individual local agents, i.e., the patients (see Figure 4.4). At the ward level where individual patients are situated and interact with each other, global variables are used to define the ward layout, the intervention policies, the common characteristics of MRSA such as the transmissibility and common features shared by all patients such as the arrival rate and proportion of patients colonised on admission.

Individual patient attributes are represented by local variables. Patient states and the behaviour rules governing the state transitions are defined by two state-charts in Anylogic®. One state-chart represents the colonisation status, detection and decolonisation treatment states of the patient and the corresponding behaviour rules that govern the changes among these states. The other state-chart represents the location states of the patient and the corresponding bed allocation and patient movement rules, including the isolation policy. The two state-charts also interact with each other since a patient's colonisation status and detection states may affect its location states (e.g., a detected colonised patient may be isolated) and vice versa (e.g., a colonised patient poses less transmission risk if he/she is isolated). The behaviour rules are represented by either pre-defined functions of the state-chart, or, for more complicated and flexible rules such as the MRSA transmission, by tailor-made Java scripts which are supported by Anylogic®.

Some behaviour rules are modelled with the help of the message exchange mechanism. For example, a patient who leaves an isolation bed may send a message to a random patient in the ward bay who is waiting to be isolated. Messages can also be exchanged between different state-charts of the same agent. For example, when a colonised patient is detected by the screening test, an ‘isolation request’ message will be sent to the location and movement state-chart of the same patient; upon receiving this message, the recipient state-chart will trigger the corresponding behaviour rule that attempts to isolate the patient.

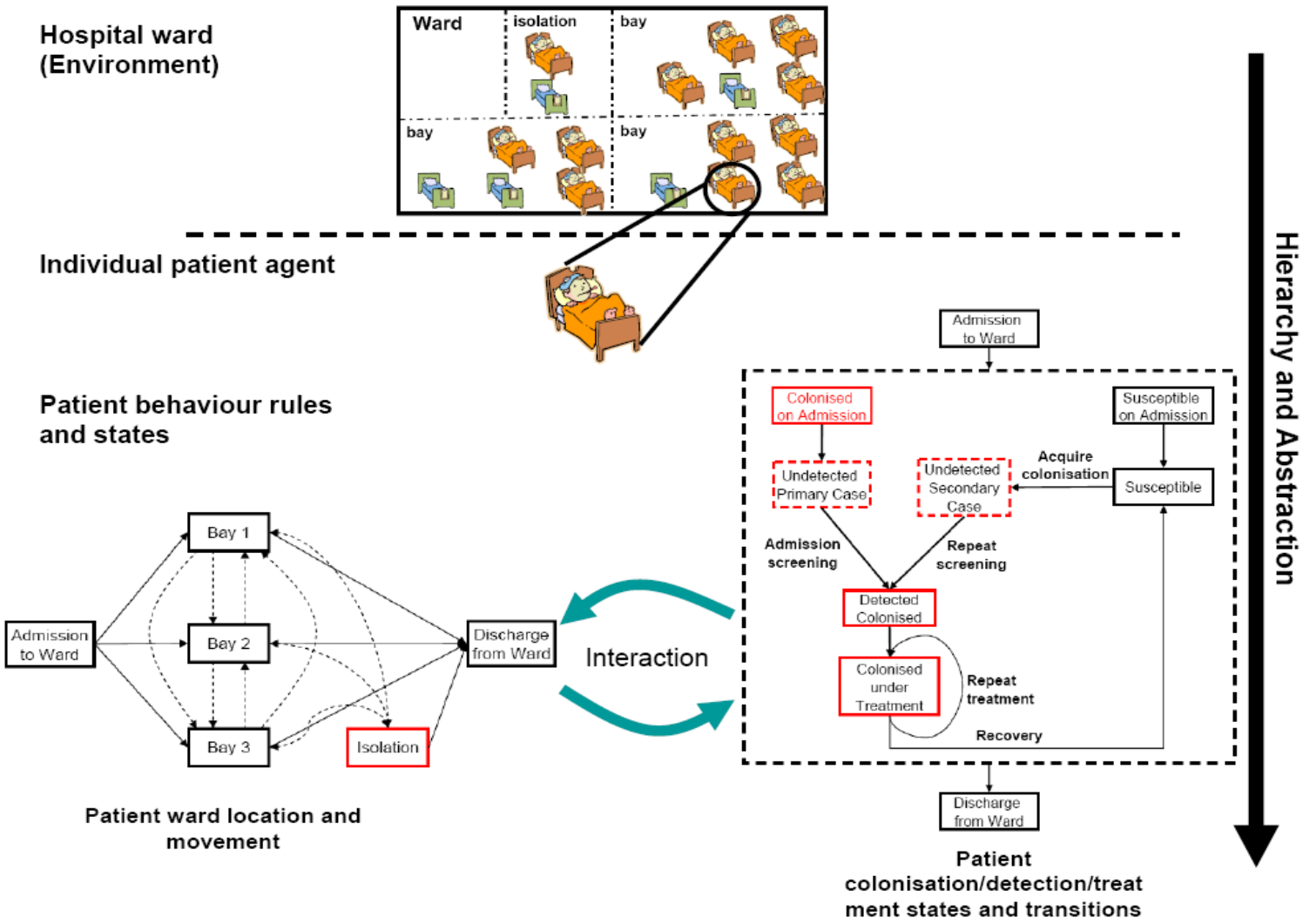

Figure 4.4 Structure of the agent-based simulation model

4.7 Summary

Applying the framework proposed in the previous chapter, this chapter presents the first known attempt to build an ABS model to study the transmission of HAIs in general and MRSA in particular. The scope of the model is a hospital ward in which each individual patient is explicitly represented as an agent which will interact with other patient agents and the ward environment. The vulnerability and infectivity of the patient are incorporated into the model. Each patient has multiple concurrent streams of states which represent colonisation, detection, decolonisation treatment and location. The transmission of MRSA is modelled between pairs of individuals in successive time-slices. Various MRSA intervention policies are embedded in the model including admission and repeat screening tests, shorter test turnaround time, isolation and decolonisation treatment.

The model will be configured with and validated against observed data from the empirical research study (see Chapter 5). Once reasonable confidence is placed on the model, the intervention policies and influencing factors will be systematically evaluated by model experimentation (see Chapter 6).

Chapter 5

Model Configuration and Validation

5.1 Introduction

In this chapter, the proposed MRSA model will be validated against empirical observation so that certain level of confidence can be placed on the model. If the model can reasonably represent or 'predict' what has happened in reality, the model can be safely applied for various 'what-if' scenarios. In this study, confidence of the model can be obtained if the predicted MRSA transmission dynamics may consistently match the observed transmission dynamics across all study wards in the hospital.

5.2 Model Configuration

The MRSA research study, on which the model was based, was carried out on seven surgical wards with a cross-over after eight months on each, creating fourteen scenarios in all. For each scenario, the model will be configured with a unique set of input parameter values based on the observed data from that particular ward and study period.

There are two main data sources for estimating the input parameter values. Whenever possible, empirical observed data from are used; but where this is not possible, previous literature, local expertise or assumptions need to be applied. One special input parameter is the transmission coefficient, the value of which will neither be directly estimated from observation nor be based on previous literature, expertise or assumptions. Instead, the value of the transmission coefficient will be determined by fitting the model to observed data during the calibration-validation process (see Section 5.3). The input parameter values can also be classified in terms of their universality:

- The values which are shared by all fourteen scenarios (e.g., transmission coefficient).
- The values which are unique for the same study ward, regardless of the study period (e.g., ward layout information)
- The values which are unique for different wards and different study periods (e.g., length of stay).

5.2.1 Input Parameter Values

In this section, the values and sources of input parameters for the model validation are estimated and discussed. Data cleaning is performed on the database of the MRSA study before they are used for the modelling study. Detailed information about data cleaning is given in Appendix C.

Ward Layout

Seven study wards that are involved in the research study have different ward layouts regarding the total number of beds in the ward, a breakdown of the number of beds in each ward bay, and the number of isolation beds in each ward. All the information about ward layout was obtained directly from the hospital (see Table 5.1).

Table 5.1 Study ward layout information

	Ward						
	A	B	C	D	E	F	G
Total beds in the ward (beds)	34	27	34	25	20	34	25
Isolation beds in the ward (beds)	2	2	4	3	2	4	3
Beds in bay 1 (beds)	6	6	6	6	6	6	6
Beds in bay 2 (beds)	6	6	6	6	6	6	6
Beds in bay 3 (beds)	6	6	6	5	6	6	5
Beds in bay 4 (beds)	7	7	6	5	n/a	6	5
Beds in bay 5 (beds)	7	n/a	6	n/a	n/a	6	n/a

Screening Test

Input parameters regarding the screening test include the actual turnaround time of the culture or rapid test for each scenario and the interval of repeat screening. The average test turnaround time for each of the fourteen scenarios is estimated directly from the observed data (see Table 5.2). According to the clinical protocol of the research study, every patient, except those who are identified as colonised with MRSA, will be screened every four days during their stay in the ward (Hardy *et al*. 2007). Therefore,

the interval for repeat screening test is set at four days across all scenarios. In the study, patients who are detected as colonised with MRSA within forty-eight hours of admission are defined as primary cases. The observed data also show that admission screening test is not always performed on the day a patient is admitted to the ward. Therefore, it is assumed that the time between the patient's admission and the admission screening follows a uniform distribution between zero and two days.

Table 5.2 Observed average test turnaround times for MRSA screening tests

Ward	A		B		C		D		E		F		G	
Study period	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po
Test turnaround time (days)	0.8	3.3	0.6	3.3	0.8	2.9	0.7	3.0	3.4	1.0	3.6	0.7	3.3	0.7

Pr: pre-crossover period; Po: post-crossover period.

Decolonisation Treatment

Input parameters regarding decolonisation treatment include the delay to the start of the treatment after the positive test result is reported, and the duration and success rate of the treatment. The average delay to the start of the treatment of each scenario is estimated from the observed data (see Table 5.3) and the actual delay in the model is sampled from the exponential distribution where the mean is set at the observed average delay.

Table 5.3 Observed average delays to the start of the decolonisation treatment after MRSA detection

Ward	A		B		C		D		E		F		G	
Study period	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po
Decolonisation treatment delay (days)	0.6	0.6	0.6	0.2	0.7	0.6	1.2	0.1	0.9	0.3	0.7	0.6	1	0.5

Pr: pre-crossover period; Po: post-crossover period.

The duration of treatment complies with the clinical protocol which is five days (Hardy *et al.* 2007). Once the treatment is over, the patient will wait for two days before being re-screened to confirm the outcome of the treatment. The treatment is deemed as successful if three successive weekly test results are negative. The average success rate of the treatment is 74.7% which is estimated from the pooled observed data and will be applied across all scenarios.

In the model, if the treatment is successful, the patient's colonisation status will change to susceptible immediately after the treatment. As the success of the treatment needs to be confirmed by three successive negative results, the patient will only move back to a ward bay (if the patient is in isolation during the treatment) once the third negative test result is reported. If the treatment fails, it is assumed that the patient will receive the treatment again once the first positive test result is reported.

Vulnerability of Susceptible Patients

Input parameters regarding vulnerability of susceptible patients include the probability of a patient being admitted to ICU, the probability of a patient being given invasive devices and the relative impacts of these risk factors on patient's vulnerability. Based on observed data, the probabilities of a patient being admitted to ICU and being given invasive devices for each scenario are estimated and shown in Table 5.4 and 5.5 respectively.

Table 5.4 Observed probability of a patient being admitted to ICU

Ward	A		B		C		D		E		F		G	
Study period	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po
ICU admission probability (%)	37.2 %	42.9 %	1.7 %	0.8 5%	7.8 %	7.1 %	1.5 %	1.1 %	3.1 %	2.9 %	5.4 %	5.1 %	1.6 %	1 %

Pr: pre-crossover period; Po: post-crossover period.

Table 5.5 Observed probability of a patient being given invasive devices

Ward	A		B		C		D		E		F		G	
Study period	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po
Invasive devices application probability (%)	86.1 %	89.2 %	62.4 %	68.7 %	78.3 %	85.7 %	79.2 %	88.3 %	75.8 %	91.3 %	77.7 %	79.1 %	73.9 %	85.8 %

Pr: pre-crossover period; Po: post-crossover period.

The relative impacts of the two risk factors are also estimated from the observed data. Patients are classified into four categories depending on the two risk factors (see 2nd and 3rd columns of Table 5.6). Based on the observed data, the relative risk of acquiring MRSA for the patients in each category is determined using standard techniques (Stewart 2002). Appendix D gives the detailed discussion of the definition of relative risk and how each relative risk is calculated. The relative risks of each

patient category are shown in the 5th column of Table 5.6. For example, compared to patients who have neither been admitted to ICU nor been given invasive devices, patients who have been admitted to ICU but not been given invasive devices are 4.6 times more likely to acquire MRSA.

The relative risks of the four categories of patient range from 1 to 6.23 which means the average risk of patients is above one. The relative risks need to be standardised so that the average risk of patients equals one, which is requested by the model (see Section 4.5.1). In order to estimate the standardised risk for each category, the proportion of patient in each category is used as the weighting factor (see the 4th column of Table 5.6). The last column of Table 5.6 shows the standardised risks of each patient category which are 0.356, 1.637, 0.826 and 2.217 respectively.

Table 5.6 The impacts of ICU admission and invasive device application on patient's vulnerability to MRSA

Patient category	ICU admission	Invasive devices application	Percentage of patients (%)	Relative risk	Weighted mean risk	Standardised risk
			a	b	Σ (a * b)	b / Σ (a * b)
1	No	No	19.4%	1	0.1942	0.356
2	Yes	No	1%	4.6	0.0441	1.637
3	No	Yes	61.3%	2.33	1.4272	0.826
4	Yes	Yes	18.4%	6.23	1.1446	2.217
Total			100%		2.81	

Length of Stay

In order to reflect the actual lengths of stay of patients during each scenario as close as possible, lengths of stay in the validation models are represented by empirical distributions rather than parametric distributions, i.e., the lengths of stay of each scenario is represented by step-wise distributions which closely follow the pattern of the observed data.

Another distinctive feature of representing the length of stay in the model is to distinguish the lengths of stay of patients who are primary cases (i.e. patients who are already colonised on admission) from those who are not. Table 5.7 shows the observed average length of stay for all patients, primary case patients, non-primary case patients, and the absolute and relative differences between the lengths of stay of

primary and non-primary case patients of each scenario. The observation shows that the average length of stay of primary case patients is significant higher than non-primary case patients in most scenarios (thirteen out of fourteen). An example of two empirical distributions (one for the lengths of stay of non-primary case patients and the other for primary case patients) which have been used to configure one of the fourteen validation models are shown in the form of histogram in Figure 5.1 and 5.2. Appendix E gives the detailed empirical distributions for all fourteen validation models.

Table 5.7 Observed mean lengths of stay for all patients, primary case patients and non-primary case patients

Ward (study period)	All patients (days)	Non-primary case patients (days)	Primary case patients (days)	Absolute difference (days)	Relative difference (%)
	a	b	c	c - b	(c – b) / b
Ward A pre	7.54	7.46	9.04	1.58	21.2%
Ward A post	7.54	7.52	8.74	1.22	16.2%
Ward B pre	3.99	3.85	10.64	6.79	176.4%
Ward B post	2.47	2.45	3.58	1.13	46.1%
Ward C pre	7.62	7.43	11.63	4.2	56.5%
Ward C post	6.68	6.61	10.50	3.89	58.9%
Ward D pre	11.50	11.19	22.36	11.17	99.8%
Ward D post	10.10	9.93	18.86	8.93	89.9%
Ward E pre	7.80	7.56	16.45	8.89	117.6%
Ward E post	6.27	6.17	8.12	1.95	31.6%
Ward F pre	7.44	7.39	9.05	1.66	22.5%
Ward F post	6.72	6.76	5.50	-1.26	-18.6%
Ward G pre	13.11	12.96	16.94	3.98	30.7%
Ward G post	10.41	10.02	24.93	14.91	148.8%

Pre: pre-crossover period; Post: post-crossover period.

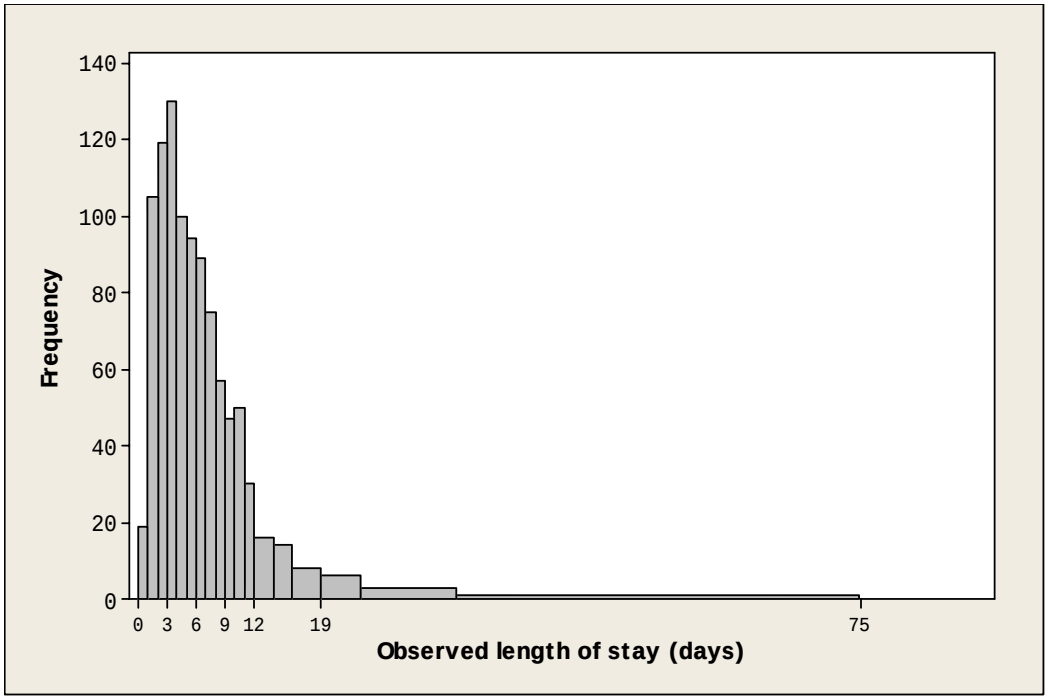

Figure 5.1 Empirical distribution of the lengths of stay of non-primary case patients for pre-crossover period of ward A

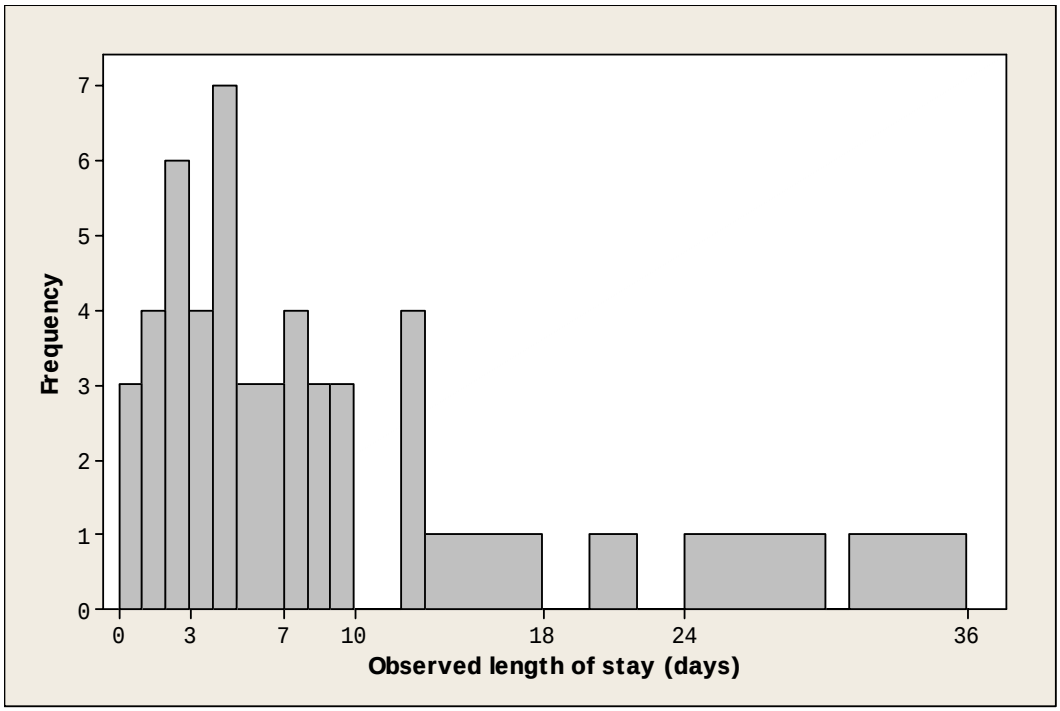

Figure 5.2 Empirical distribution of the lengths of stay of primary case patients for pre-crossover period for ward A

Arrival Rate and Endemic Setting

Patient arrival rates for all scenarios are directly estimated from observed data by dividing the total number of days in the study period by the corresponding total number of admissions in that period (see Table 5.8). The proportion of patients

colonised with MRSA on admission, or the endemic setting, of each scenario is also estimated from observed data by dividing the number of primary cases by the total number of admissions in each scenario (Table 5.8).

Table 5.8 Observed patient arrival rate and proportion of patients colonised with MRSA on admission

Ward (study period)	Total admissions	Study period (days)	Patient arrival rate (patients per day)	Primary cases	Endemic setting (%)
	a	b	c = a / b	d	e = d / a
Ward A pre	1088	243	4.48	58	5.3%
Ward A post	997	242	4.12	18	1.8%
Ward B pre	894	243	3.68	22	2.5%
Ward B post	1933	242	7.99	27	1.4%
Ward C pre	1070	243	4.40	60	5.6%
Ward C post	1050	242	4.34	32	3.0%
Ward D pre	479	243	1.97	17	3.5%
Ward D post	543	242	2.24	16	2.9%
Ward E pre	638	243	2.63	29	4.5%
Ward E post	788	242	3.26	43	5.5%
Ward F pre	1065	243	4.38	41	3.8%
Ward F post	1171	242	4.84	49	4.2%
Ward G pre	445	243	1.83	24	5.4%
Ward G post	521	242	2.15	17	3.3%

Pre: pre-crossover period; Post: post-crossover period.

Availability of Isolation Beds

The isolation beds in the ward are not solely reserved for MRSA patients. Patients who are identified to have other infectious diseases (e.g., *C. difficile*) or require special clinical care may also occupy the isolation facilities. The parameter of isolation bed availability reflects the probability that detected MRSA patients can not be isolated due to such reasons. The parameter values are estimated from the observed data (see Table 5.9). For example, for ward A during the pre-crossover period, the probability that a detected MRSA patient can be successfully isolated is 23.8%.

Table 5.9 Observed availability of isolation beds

Ward	A		B		C		D		E		F		G	
Study period	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po	Pr	Po
Isolation bed availability (%)	23.8 %	35.7 %	31.5 %	25.0 %	9.8 %	41.0 %	10.0 %	36.4 %	14.9 %	18.3 %	22.6 %	18.1 %	22.6 %	5.4 %

Pr: pre-crossover period; Po: post-crossover period.

Assumed Values for Other Parameters

Apart from the transmission coefficient, key model assumptions including *m* (proportion of transmission risk coming from within the same bay compared to the whole ward), *k* (effectiveness of decolonisation treatment) and *s* (inter-bay movement rate) are derived from local expertise and assumptions, and share the same value across all scenarios for model validation. It is assumed that roughly two thirds of the transmission risk is caused within the same bay due to local interactions while the rest of the risk is determined by the ward-level interactions. Therefore, the parameter of *m* is set at 0.667. The parameter of *k* is set at 0.4 for patients undergoing decolonisation treatment. It assumes that colonised patients who receive decolonisation treatment may reduce their infectivity by 60%. Since the values of both parameters are based on assumptions, sensitivity analysis will be performed on both *m* and *k* during model experimentation. The parameter of *s* is set at 0.1 which assumes, on average, a patient is moved from one bay to another every ten days during the ward stay. The actual interval between each inter-bay movement is sampled from an exponential distribution with a mean interval of 10 days. Table 5.10 summaries the input parameter values of the fourteen validation models.

Table 5.10 Summary of input parameter values for model validation

Category	Parameter name		Parameter values													
			A		B		C		D		E		F		G	
			pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
Ward layout	Total beds in a ward (beds)		34		27		34		25		20		34		25	
	Isolation beds in a ward (beds)		2		2		4		3		2		4		3	
	Beds in bay1 (beds)		6		6		6		6		6		6		6	
	Beds in bay2 (beds)		6		6		6		6		6		6		6	
	Beds in bay3 (beds)		6		6		6		5		6		6		5	
	Beds in bay4 (beds)		7		7		6		5		n/a		6		5	
	Beds in bay5(beds)		7		n/a		6		n/a		n/a		6		n/a	
Screening test	Test turnaround time(days)		0.8	3.3	0.6	3.3	0.8	2.9	0.7	3	3.4	1	3.6	0.7	3.3	0.7
	Repeat screening interval (days)		4													
Decolonisation treatment	Delay of treatment (days)		0.6	0.6	0.6	0.2	0.7	0.6	1.2	0.1	0.9	0.3	0.7	0.6	1	0.5
	Treatment duration (days)		5													
	Treatment success rate (%)		74.7%													
Vulnerability	Probability admitted to ICU (%)		37.2%	42.9%	1.7%	0.85%	7.8%	7.1%	1.5%	1.1%	3.1%	2.9%	5.4%	5.1%	1.6%	1%
	Probability of giving invasive device (%)		86.1%	89.2%	62.4%	68.7%	78.3%	85.7%	79.2%	88.3%	75.8%	91.3%	77.7%	79.1%	73.9%	85.8%
	Impact on vulnerability due to ICU admission and invasive devices application	V	0.356 (No ICU admission and No invasive devices applications)													
			1.637 (ICU admission but No invasive device applications)													
			0.826 (No ICU admission but invasive device application)													
			2.217 (ICU admission and invasive devices application)													
Length of stay	All patients LOS (days)		7.05	7.05	3.55	2.06	7.15	6.2	11.01	9.61	7.32	5.78	6.96	6.24	12.62	10.41
	Non-primary case patients LOS (days)		6.97	7.04	3.41	2.04	6.95	6.13	10.7	9.45	7.07	5.69	6.91	6.28	12.47	10.02
	Primary case patients LOS (days)		8.56	8.24	10.14	3.22	11.16	10	21.86	18.41	15.95	7.62	8.56	5.01	16.47	24.93

Other information	Patient arrival rate (patients per day)		4.48	4.12	3.68	7.99	4.4	4.34	1.97	2.24	2.63	3.26	4.38	4.84	1.83	2.15
	Endemic setting (%)		5.3 %	1.8 %	2.5 %	1.4 %	5.6 %	3%	3.5 %	2.9 %	4.5 %	5.5 %	3.8 %	4.2 %	5.4 %	3.3 %
	Availability of isolation beds (%)		23.8 %	35.7 %	31.5 %	25.0 %	9.8 %	41.0 %	10.0 %	36.4 %	14.9 %	18.3 %	22.6 %	18.1 %	22.6 %	5.4 %
Other model assumptions	Transmission coefficient	*C*	To be fitted with observed data													
	Proportion of risk within bay	*m*	0.667													
	Treatment effect on infectivity	*k*	0.4													
	Inter-bay movement rate	*s*	0.1													

Pre: pre-crossover period; Post: post-crossover period; LOS: length of stay.

5.2.2 Data for Model Validation

Empirical observation that will be compared to model responses includes the actual number of secondary cases, the transmission ratio and the "average time to detection" of each scenario (see Table 5.11). The number of secondary cases is obtained from the observed data and the transmission ratio which is the ratio of the secondary case to the primary case is calculated (see Table 5.8). For each detected MRSA patient, the time to detection measures the delay between the time the patient is admitted to the ward and the time the patient is detected as colonised with MRSA. For each scenario, the average time to detection is estimated from the observed data.

Table 5.11 Observed data to be compared with model responses

Ward (study period)	Secondary cases	Transmission ratio	Average time to detection (days)
Ward A pre	18	0.31	10.7
Ward A post	36	2.00	12.8
Ward B pre	6	0.27	14.2
Ward B post	4	0.15	8.3
Ward C pre	34	0.57	15.4
Ward C post	20	0.63	13.8
Ward D pre	8	0.47	19.3
Ward D post	11	0.69	9.7
Ward E pre	36	1.24	13.4
Ward E post	15	0.35	8.1
Ward F pre	38	0.93	13.8
Ward F post	23	0.47	13.4
Ward G pre	12	0.50	13.4
Ward G post	7	0.41	6.4

Pre: pre-crossover period; Post: post-crossover period.

5.3. Model Validation

Regarding the validation of epidemiological models, Cooper (2007) argued that the best we are able to say is that we can not reject the model following confrontations with observed data, and we will expect to gain more confidence in a model that repeatedly passes such a test. One advantage of this study is that there is a large amount of observed data and more importantly, there are fourteen separate scenarios based on which the model can be repeatedly tested and validated. In each scenario, input parameter values that are derived mainly from the empirical data are used to configure the model and the dynamic model responses will, in turn, be compared with

the corresponding observations. Such repeated model validation tests are beneficial to gain confidence in the model, and have seldom been carried out in previous HAI modelling studies due to the lack of observed data.

5.3.1 Validation Method

Chance Effect and Multiple Replication Simulation Runs

Chance effect or randomness is one of the key features of HAIs (see Section 1.2.2). Given the same initial conditions, the transmission dynamics may be very different simply due to the intrinsic stochasticity of the spread of infectious diseases within a small patient population. Figure 5.3 demonstrates two different transmission dynamics realised by two simulation runs with exactly the same initial conditions and input parameter values. Due to chance effects, conclusions drawn from simulation models, either for model validation or experimentation, must be based on multiple replications so that the mean and the variations of model responses can be estimated. Therefore, it was decided that 500 replications of simulation runs should be performed for each distinctive set of input parameter values during model validation and experimentation. Furthermore, in order to get rid of the initial bias, a warm-up period of 50 days is added for each simulation run and consequently only simulation data after 50 days are collected for analysis. The time needed to run a single replication of the model for a year was about 1 second on a personal computer with a 2.2GHz Intel processor.

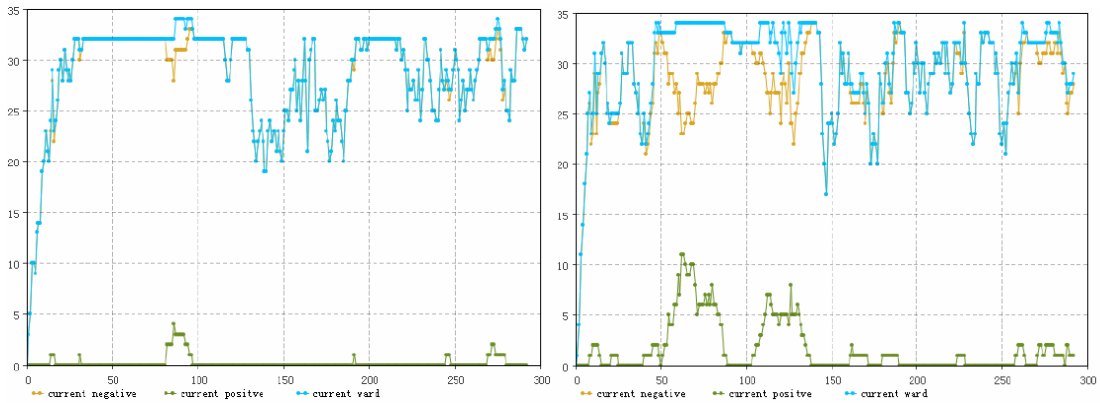

Figure 5.3 Realisation of two transmission dynamics by two simulation runs with the same initial condition and input parameter values (blue line: number of total patients in the ward; brown line: number of susceptible patients in the ward; green line: number of colonised patients in the ward)

To demonstrate that the hospital ward has settled into a steady state after 50 days, Figure 5.4 shows the time-series of the mean number of patients in the hospital ward from 30 replications. The model is configured with model inputs of ward A during the pre-crossover period (see Table 5.10) assuming a transmission coefficient of 0.1. Figure 5.4 indicates that the mean number patients in the hospital ward increases from zero (the hospital ward is empty at the beginning of the simulation) to about 31 during the first 50 days; afterwards the mean number of patients levels off and varies in a small range between 29 and 33 patients.

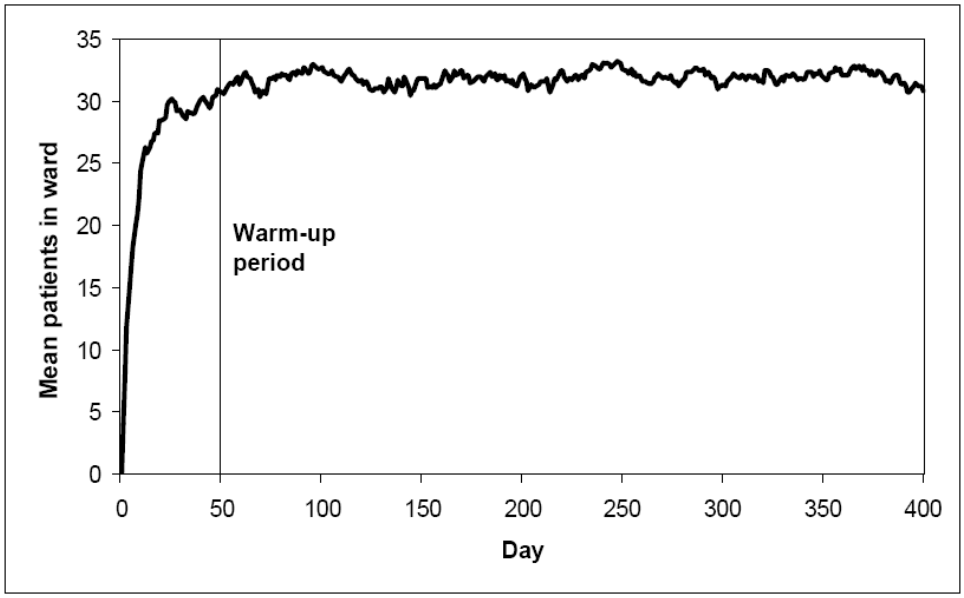

Figure 5.4 Time-series of the mean number of patients in the hospital ward from 30 replications

To demonstrate that 500 replications are enough to obtain accurate model responses, the confidence interval method is applied (Robinson 2004). Figure 5.5 shows the cumulative mean and the confidence interval of the transmission ratio from 1000 replications of the model configured with inputs of ward A during the pre-crossover period assuming a transmission coefficient of 0.1. A significant level of 5% is used to construct the confidence interval which ensures a 95% probability that the value of the 'true' mean transmission ratio lies within the calculated confidence interval. For each replication, the simulation is run for 415 days with 50 days warm-up period and 365 days for data collection. Figure 5.5 demonstrates that the confidence interval is sufficiently narrow and the cumulative mean line (the thick line in the middle) becomes almost a flat line after 500 replications are performed. The precision of the

model response, which is defined as half the width of the confidence Interval expressed as a percentage of the cumulative mean (Robinson 2004), is about 1.9% after 500 replications.

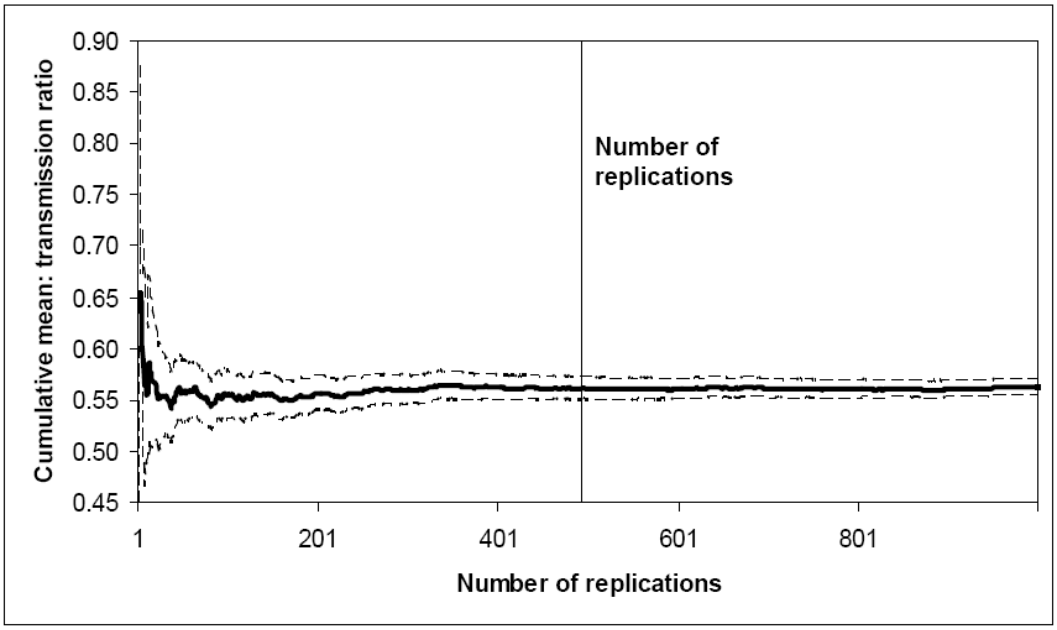

Figure 5.5 Cumulative mean and confidence interval of the transmission ratio from 1000 replications

The Calibration-Validation Process

The procedure to validate the model follows the calibration-validation process, in which all fourteen scenarios are randomly split up into two groups, one for the parameter calibration process and the other for the model validation process.

The only parameter to be calibrated is the transmission coefficient which is defined as the number of secondary cases incurred by one primary case per day assuming a large population of susceptible patients in the system. The transmission coefficient is the key parameter to define the transmission dynamics of infectious diseases. However, it is also difficult to estimate the parameter directly from observation (Cooper and Lipsitch 2004). As a result, the transmission coefficient has been the subject of many previous modelling studies in which mathematical compartmental models were fitted to observed data to calibrate the coefficient (Grundmann *et al.* 2002; Pelupessy *et al.* 2002; Cooper and Lipsitch 2004; Forrester *et al.* 2005).

During the following model validation stage, the transmission coefficient calibrated in the calibration stage will be applied to the rest of the scenarios, and comparisons between observations and model responses will be performed to determine how close the model can represent the real system.

Parameter Calibration

During parameter calibration, the best estimate of the transmission coefficient for each scenario in the calibration group is estimated. All these best estimates of the transmission coefficient will then be used calculate the overall transmission coefficient for the following validation stage.

For each calibration scenario, the transmission coefficient is tested on a range of values to find the best-fit coefficient that leads to the closest match between the observed transmission ratio and the mean transmission ratio predicted by the model through 500 replications. During parameter calibration, all other input parameters, except the transmission coefficient, will take the values given in Table 5.10.

In order to find the best estimate of the transmission coefficient for each scenario, the coefficient is initially set at 0.1 which is an arbitrary value based on the estimations from previous studies (Hotchkiss *et al.* 2005; McBryde *et al.* 2007). Starting with the initial values, the model is run for 500 replications and the mean predicted transmission ratio is compared with the observed transmission ratio (see Table 5.11). If the former is larger than the latter, which indicates that the coefficient in the current model is too high, the coefficient is decreased by one small unit and the comparison will be repeated. Otherwise, if the mean transmission ratio is smaller than what is observed, which indicates the coefficient in the current model is too low, the comparison will be repeated with the coefficient being increased by one small unit. The small unit chosen in the study is 0.001. This iterative process continues until two consecutive comparisons give two distinctive results with one showing mean model response is slightly higher than the observation and the other showing the opposite. The search will stop at this point and the coefficient which gives the smaller absolute difference between the mean model response and the observation is chosen to be the best estimate of the transmission coefficient for this scenario.

Once the estimates of the transmission coefficient from all scenarios in the calibration group are obtained, a weighted mean coefficient is calculated to be the overall transmission coefficient. In this study, the number of secondary cases in each scenario is selected as the weighting factor since it is a reasonable indicator of the magnitude of MRSA transmission in each scenario and the data are available from observation.

Model Validation

During the model validation stage, the weighted mean transmission coefficient determined in the calibration stage will be used to test the fit of the model to the observed data for all scenarios in the validation group. For each scenario, the model will be run for 500 replications and the mean and distribution of various model responses (not only the transmission ratio, but also the absolute number of secondary cases and the average time to detection) will be compared with the corresponding observations.

Due to chance effects, each observed scenario is just one possible realisation which may take place for that ward during that study period with the same input parameter values. Therefore, the single observation itself does not necessarily represent the theoretical average transmission dynamics and it may even be an extreme case. As Robinson (2004) argued that real world data, even if "accurate", are only a sample which in itself creates inaccuracy. Therefore, when a single outcome from the observation (e.g., the observed transmission ratio of one scenario) is compared with the corresponding model responses (e.g., the mean and distributions of transmission ratios predicted by 500 replications of the same scenario), they are unlikely to be an exact match.

In order to compare rationally a single observation with the corresponding model responses, it is reasonable to look at whether the single observation is within certain range of the model responses (e.g., within two standard deviations, or within first and third quartiles). The practice has been used for the validation of HAI models (Austin *et al.* 1999; Grundmann *et al.* 2002). In this study, for each validation scenario, the single observation will be compared with the first and third quartiles, and tenth and ninetieth percentiles of the model responses from 500 replications. Standard deviation is not used for the comparisons since the model responses do not follow the normal

distribution (see Section 5.3.2). Paired-t statistical tests are also applied to test the difference between the observed and mean model responses.

5.3.2 Validation Results

Among the fourteen scenarios from the research study, one scenario, which corresponds to the post-crossover study period of ward A, is excluded from the validation analysis since the ward was closed for refurbishment for a couple of months in that period and the number of isolation beds was changed after the refurbishment.

In order to reduce the bias from certain wards and ensure that both calibration and validation sample groups can be a fair representation of all study wards, every scenario in the calibration group must come from a different ward. The result of the sample split-up was that the pre-crossover period of ward A, E and G, and the post-crossover period of ward B, D and F are used for the parameter calibration stage; while the remaining seven scenarios are used for the model validation stage.

Parameter Calibration

For each scenario in the calibration group, the procedure described in Section 5.3.1 is applied to find one best estimate of the theoretical transmission coefficient. Table 5.12 shows each estimate of the transmission coefficient from the calibration scenarios and the weighted mean transmission coefficient which is used for the validation stage. The numbers of secondary cases used to weight each estimate of the transmission coefficient are also given in the table. The six estimates of the transmission coefficient range from 0.063 to 0.180 and the weighted mean coefficient is 0.1404.

Table 5.12 Parameter calibration for transmission coefficient

Ward	Study period	Type of screening test	Estimate of C	Observed secondary cases		Weighted mean C
			a	b	b * a	$\frac{\sum(b \times a)}{\sum b}$
A	Pre	PCR	0.063	18	1.134	
B	Post	Culture	0.105	4	0.420	
D	Post	Culture	0.151	11	1.661	
E	Pre	Culture	0.180	36	6.480	
F	Post	PCR	0.162	23	3.726	
G	Pre	Culture	0.098	12	1.176	
				104	14.597	0.1404

Pre: pre-crossover period; Post: post-crossover period; C: transmission coefficient.

Model Validation – Comparison between Observation and Model Responses

The weighted mean transmission coefficient is used for all seven scenarios in the model validation group. 500 replications are performed for each scenario and the model predictions are compared with the observed transmission ratio, number of secondary cases and the average time to detection.

Normality tests are performed to ascertain whether the 500 individual model responses of the transmission ratio in each scenario follow a normal distribution. The tests were carried out in MINITAB® and the methods applied include the Anderson-Darling test, the Ryan-Joiner Test and the Kolmogorov-Smirnov test. The null hypothesis (Ho) of the test is that the model responses follow a normal distribution, while the alternative hypothesis (Ha) is that the model responses do not follow a normal distribution. The test results are shown in Table 5.13. For every validation scenario and every normality test method (except for the post-crossover period for Ward E using the Anderson-Darling and Kolmogorov-Smirnov tests), the null hypothesis is rejected under the significant level of 5% (i.e., the individual transmission ratios predicted by the model do not follow a normal distribution). Therefore, a non-parametric method based on quartiles is used.

Table 5.13 Normality tests for model responses of transmission ratio from 500 replications

Ward (Study period)	Anderson-Darling Test		Ryan-Joiner Test		Kolmogorov-Smirnov Test		Conclusion
	p-value	Reject Ho	p-value	Reject Ho	p-value	Reject Ho	
Ward B (Pre)	0	Yes	<0.01	Yes	<0.01	Yes	Not Normal
Ward C (Pre)	0	Yes	<0.01	Yes	<0.01	Yes	Not Normal
Ward C (Post)	0	Yes	<0.01	Yes	<0.01	Yes	Not Normal
Ward D (Pre)	0	Yes	<0.01	Yes	<0.01	Yes	Not Normal
Ward E (Post)	0.08	No	0.037	Yes	>0.15	No	Hard to say
Ward F (Pre)	0	Yes	<0.01	Yes	0.047	Yes	Not Normal
Ward G (Post)	0	Yes	<0.01	Yes	<0.01	Yes	Not Normal

Pre: pre-crossover period; Post: post-crossover period.

Figure 5.6 shows the distribution of the 500 individual transmission ratios predicted by the model (i.e., the histogram) for one validation scenario (ward C during the pre-crossover period). The first and third quartiles (0.423 and 0.608), the tenth and ninetieth percentiles (0.356 and 0.709) of the predicted transmission ratios and the observed transmission ratio (0.567) are also shown in the diagram. For this validation scenario, the observed transmission ratio lies between the first and third quartiles of the predicted transmission ratios, indicating a fairly good match between the observation and the model prediction.

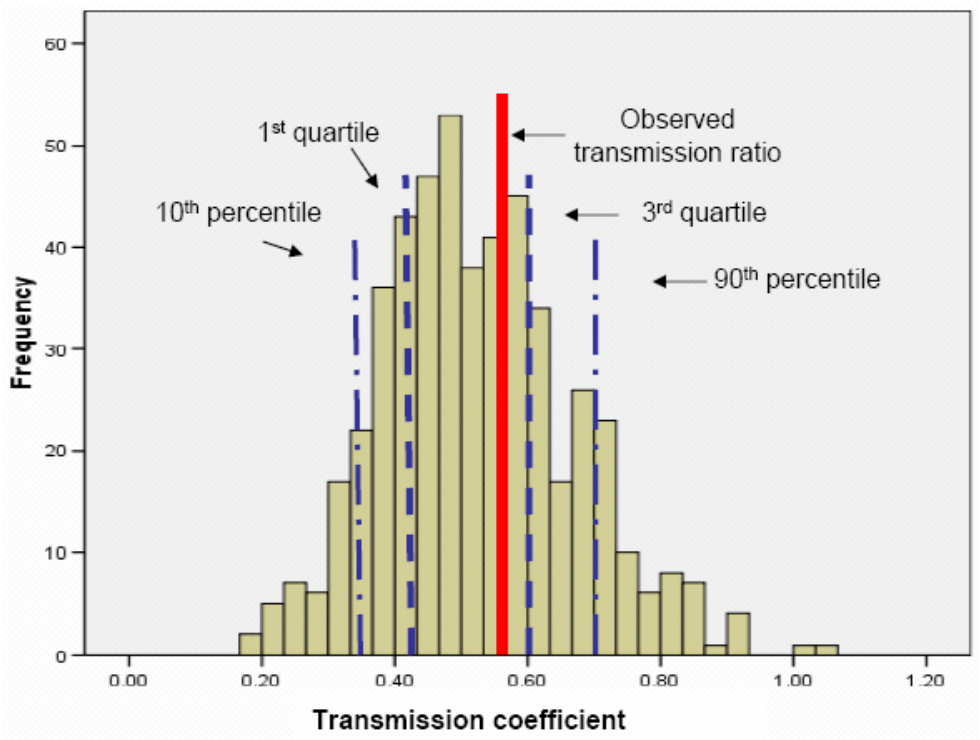

Figure 5.6 Comparison between observed transmission ratio and transmission ratios predicted by multiple replications of the simulation model (pre-crossover period of ward C)

Spider diagrams are used to show the comparisons of all seven validation scenarios in a single diagram. Figure 5.7, 5.8 and 5.9 show the comparisons between observations and model predications regarding the transmission ratio, the absolute number of secondary cases and the average time to detection respectively. The data behind the spider diagrams and the comments on the closeness between the observation and model predictions are shown in Table 5.14, 5.15 and 5.16.

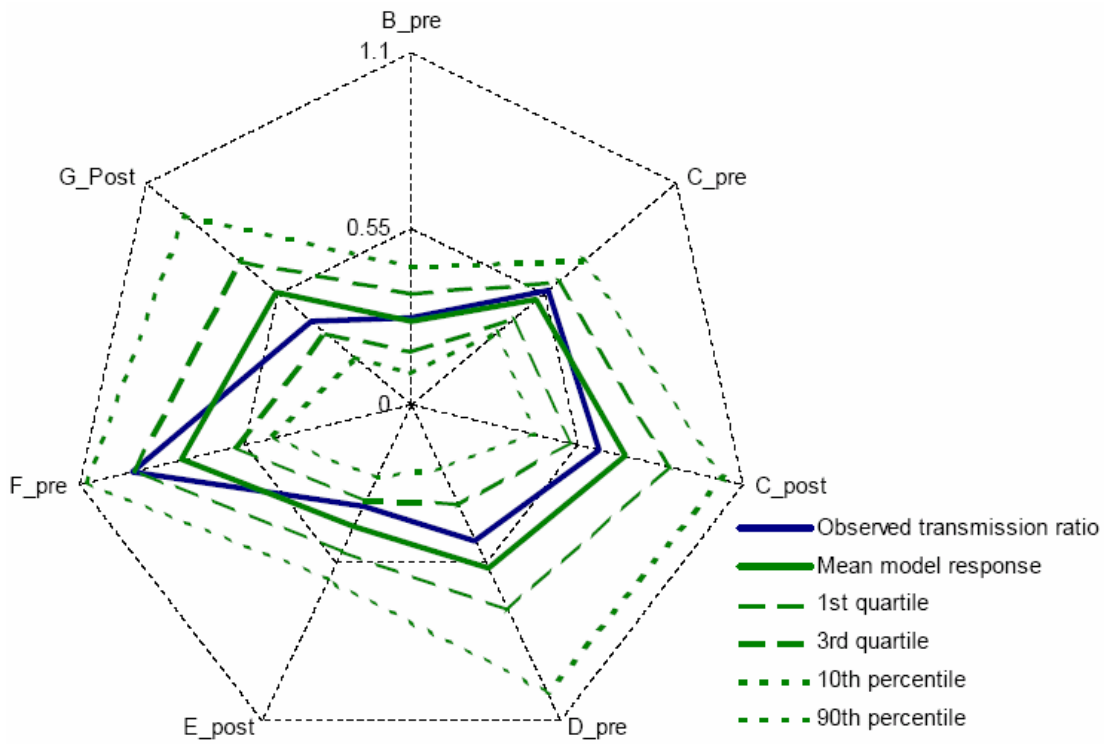

Figure 5.7 Comparison between observed transmission ratio and model predications

Table 5.14 Comparison between observed transmission ratio and model predications

Ward (Study period)	Obser vation	Mean model responses	1st quartile	3rd quartile	10th percentile	90th percentile	Remark
Ward B (Pre)	0.273	0.259	0.167	0.345	0.095	0.429	Within quartiles
Ward C (Pre)	0.567	0.524	0.423	0.608	0.356	0.709	Within quartiles
Ward C (Post)	0.625	0.706	0.526	0.857	0.406	1.036	Within quartiles
Ward D (Pre)	0.471	0.565	0.347	0.714	0.222	1.000	Within quartiles
Ward E (Post)	0.349	0.425	0.332	0.511	0.250	0.607	Within quartiles
Ward F (Pre)	0.927	0.759	0.587	0.917	0.459	1.08	Within percentiles
Ward G (Post)	0.412	0.561	0.35	0.71	0.235	0.942	Within quartiles

Pre: pre-crossover period; Post: post-crossover period.

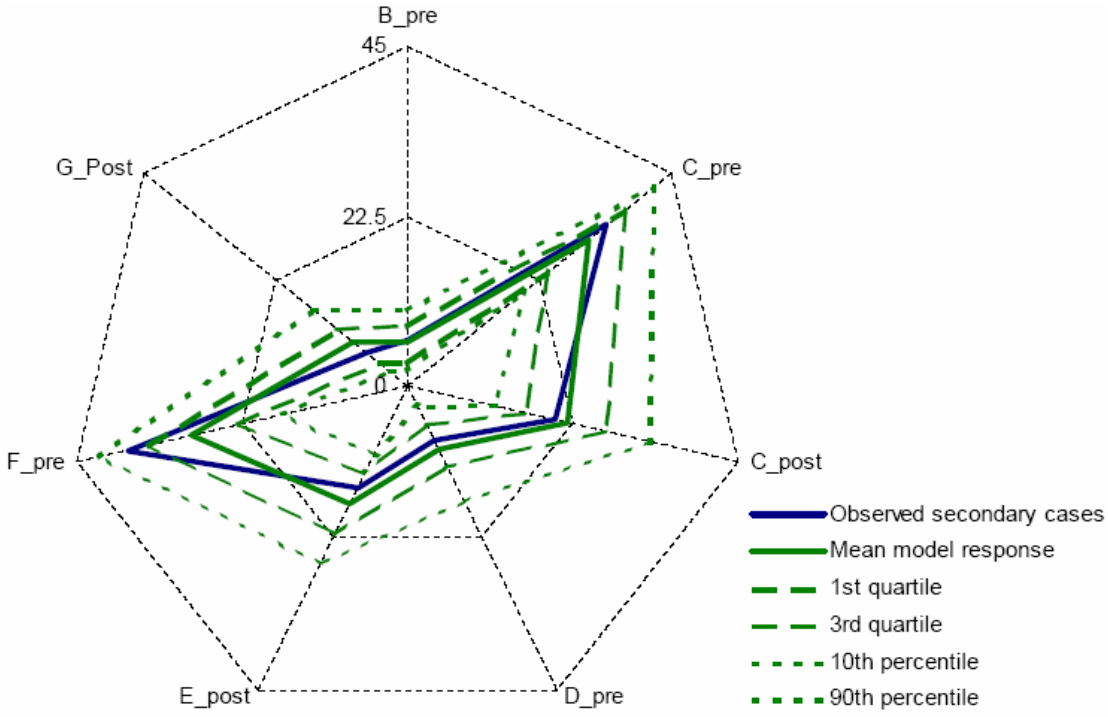

Figure 5.8 Comparison between observed number of secondary cases and model predications

Table 5.15 Comparison between observed number secondary cases and model predications

Ward (Study period)	Obser vation	Mean model responses	1st quartile	3rd quartile	10th percentile	90th percentile	Remark
Ward B (Pre)	6	5.8	3	8	2	10	Within quartiles
Ward C (Pre)	34	30.7	24	37	20	42	Within quartiles
Ward C (Post)	20	21.7	16	27	12	33	Within quartiles
Ward D (Pre)	8	9.3	5.8	12	3	17	Within quartiles
Ward E (Post)	15	17.5	13	22	10	26.1	Within quartiles
Ward F (Pre)	38	29.4	23	35.3	17	42	Within percentiles
Ward G (Post)	7	9.3	5	12	3	16	Within quartiles

Pre: pre-crossover period; Post: post-crossover period.

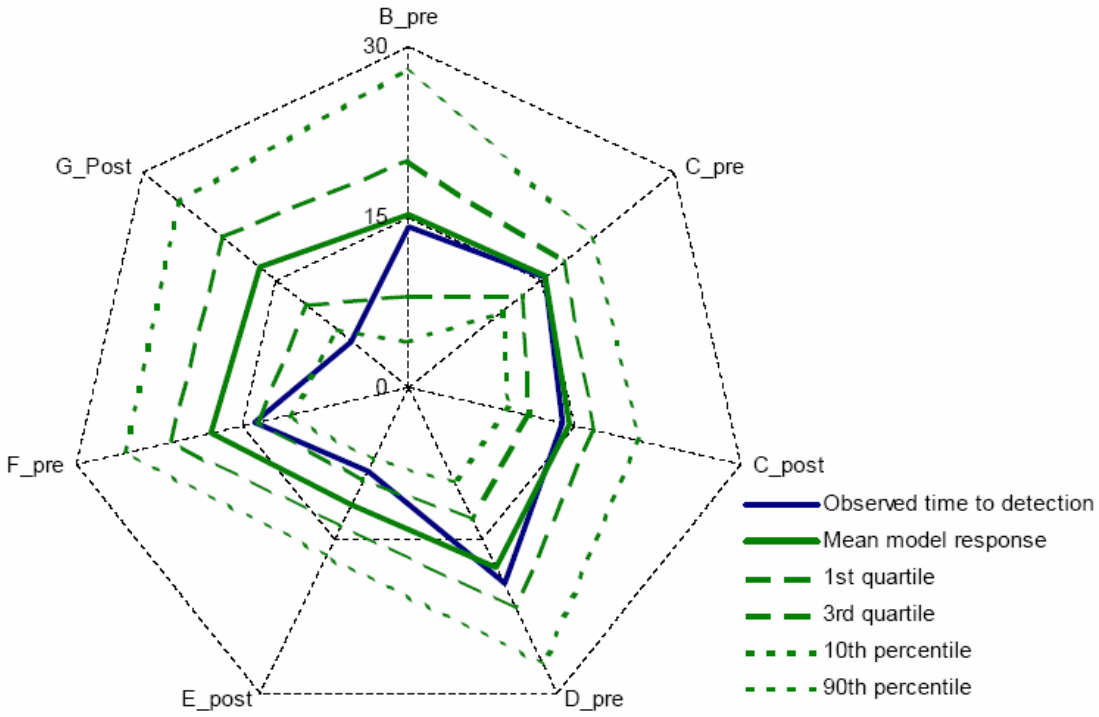

Figure 5.9 Comparison between observed average time to detection and model predications

Table 5.16 Comparison between observed average time to detection and model predications

Ward (Study period)	Obser vation	Mean model responses	1st quartile	3rd quartile	10th percentile	90th percentile	Remark
Ward B (Pre)	14.2	15.2	8	20	4	28	Within quartiles
Ward C (Pre)	15.4	15.5	12.8	17.7	10.6	20.8	Within quartiles
Ward C (Post)	13.8	14.4	10.9	16.7	8.9	20.7	Within quartiles
Ward D (Pre)	19.3	17.7	12.7	21.6	9.3	27	Within quartiles
Ward E (Post)	8.1	11.5	9.1	13.6	7	16.4	Within percentiles
Ward F (Pre)	13.8	17.8	13.6	21.5	10.8	25.5	Within quartiles
Ward G (Post)	6.4	16.8	11.6	20.9	8	26	Within range

Pre: pre-crossover period; Post: post-crossover period.

The comparison between the empirical observations and the model predictions are encouraging. Regarding the transmission ratio and the number of secondary cases, the observed data are within the first and third quartiles of the model prediction in six out of seven scenarios and within the tenth and ninetieth percentile in one scenario. This is an indication that the model may correctly and consistently predict and match the actual transmission dynamics under a wide variety of situations (e.g., the average length of stay of the seven validation scenarios ranges from 3.55 to 11.01 days, the total ward size and the number of isolation beds ranges from 20 to 34 beds and from 2

to 4 beds respectively, and the proportion of colonised patients on admission ranges from 2.5% to 5.6%).

As to the validation on the average time to detection, the observed data are within the first and third quartiles of model predictions in five out of seven scenarios, within the tenth and ninetieth percentiles in one scenario, and within range in one scenario. Though not as strong a match as the comparisons for the transmission ratio and the number of secondary cases, it still demonstrates the capability of the model to consistently predict the actual transmission dynamics in a more detailed and micro level. It is the first time a HAI model captures the patient-level statistics of time to detection and compares it with observed values.

Overall, reasonable confidence can be placed on the validity of the model as the model might be correctly and consistently matching the actual MRSA transmission dynamics not only on a single scenario, but across all seven validation scenarios.

Model Validation – Statistical Tests

Apart from comparisons through diagrams and tables, statistical tests were performed to test whether there is a significant difference between the observation and the mean model responses. The statistical method applied is the paired-t test which is suitable to test the difference of the means from two dependent samples that are of the same sample size and consist of matched pairs. Each of the seven scenarios in the validation group will produce a matched pair and hence each paired-t test involves seven matched pairs. Within each pair, one variable is the observed transmission ratio (or observed number of secondary cases, or observed average time to detection) and the other dependent variable is the corresponding mean transmission ratio (or mean number of secondary cases, or mean average time to detection) predicted by the model.

Confidence intervals (under the confidence level of 99% and 95%) of the difference between the observation and the mean model prediction were constructed by the statistical package MINITAB® using the paired-t test. If the confidence interval includes zero, it means, under the chosen confidence level, there is no significant difference between the observation and the mean model prediction; otherwise, it

indicates the difference between the observation and the model prediction is statistical significant.

Table 5.17 reports the results of the paired-t tests using the data shown in the second and third columns of Table 5.14, 5.15 and 5.16 (the second column gives the observed transmission ratio, number of secondary cases and average detection time, while the third column gives the corresponding mean model predictions). The confidence intervals constructed all include zero which demonstrates that, under the confidence level of 99% and 95%, there is no statistical significant difference between the observation and mean model predictions.

The p-values of the paired-t tests are also given in Table 5.17. The higher the p-value is, the more likely not to reject the null hypothesis that there is no difference between the observation and the mean model predictions. P-values for the transmission ratio and the number of secondary cases are very high (0.561 and 0.702) which is a strong indication that there is no statistical difference between observed transmission ratio (and number of secondary cases) and the mean model predications.

Table 5.17 Results of paired-t tests for the difference between observation and model predictions

Paired-t test	99% confidence interval	95% confidence interval	p-value	Conclusion
Transmission ratio	(-0.176 , 0.126)	(-0.124 , 0.074)	0.561	No difference
Number of secondary cases	(-5.06 , 6.29)	(-3.13 , 4.36)	0.702	No difference
Average time to detection	(-8.10 , 2.99)	(-6.22 , 1.10)	0.138	No difference

5.3.3 Final Estimation of the Transmission Coefficient

As reasonable confidence has been gained on the validity of the model by the calibration-validation process, a final task in this chapter is to estimate the weighted mean transmission coefficient again using all thirteen scenarios (one scenario is excluded from analysis as explained in Section 5.3.2) rather than just the six scenarios in the calibration group. Compared to the previously calibrated transmission coefficient based on six scenarios, this final transmission coefficient should, in theory, be closer to the true theoretical transmission coefficient of the MRSA study since it is based on all available scenarios. The final transmission coefficient will be used to

configure the hypothetical test ward based on which formal and systematic model experimentations will be carried out in Chapter 6.

The final weighted mean transmission coefficient calculated is 0.1414 (see Table 5.18), which, due to the large amount of empirical data involved and the reasonable confidence that has been placed on the model, can also be a reasonable estimation of the MRSA transmission coefficient of a typical surgical ward in the UK hospitals. This value complies with the findings or the values used by previous modelling studies (Grundmann *et al.* 2002; Cooper *et al.* 2004; Bootsma *et al.* 2006; McBryde *et al.* 2007) and it may be used in future MRSA modelling studies where the value of the transmission coefficient is required to configure the model.

Table 5.18 Estimation of final weighted mean transmission coefficient based on all scenarios

Ward	Study period	Type of screening test	Unique *C*	Observed secondary cases		Weighted mean *C*
			a	b	b * a	$\frac{\sum(b \times a)}{\sum b}$
A	Pre	PCR	0.063	18	1.134	
B	Pre	PCR	0.144	6	0.864	
B	Post	Culture	0.105	4	0.42	
C	Pre	PCR	0.15	34	5.1	
C	Post	Culture	0.132	20	2.64	
D	Pre	PCR	0.123	8	0.984	
D	Post	Culture	0.151	11	1.661	
E	Pre	Culture	0.18	36	6.48	
E	Post	PCR	0.12	15	1.8	
F	Pre	Culture	0.159	38	6.042	
F	Post	PCR	0.162	23	3.726	
G	Pre	Culture	0.098	12	1.176	
G	Post	PCR	0.111	7	0.777	
				232	32.804	0.1414

Pre: pre-crossover period; Post: post-crossover period.

5.3.4 Conclusions

It is the first time that a MRSA transmission model is systematically validated against observed data using formal model validation methods. Robinson (2004) argued that it is not possible to prove that a model is absolutely valid and instead it is only possible to think in terms of the confidence that can be placed in a model. As the model appears to be correctly and consistently matching the actual transmission dynamics

across most of the validation scenarios (which represent a variety of situations regarding length of stay, ward size, endemic setting and other features), reasonable confidence can be placed on the model.

There are some important model parameters, such as m (i.e., the proportion of transmission within the same bay compared to the whole ward), k (the effectiveness of decolonisation treatment on reducing infectivity), whose values are based on assumptions rather than empirical observation. The choice of the values of these input parameters may affect the estimation of the transmission coefficient and hence the validation results. In order to understand the extent of impacts of these parameters on model responses, sensitivity analysis will be performed on these model inputs in the following chapter.

Chapter 6

Model Experimentation and Analysis

6.1 Introduction

The purpose of model experimentation is to evaluate the effectiveness and robustness of various intervention polices to prevent and control MRSA, and to test the sensitivity of various influencing factors that have a potential impact on MRSA transmission. In particular, the chapter aims to test the effectiveness of three intervention policies: introducing rapid screening tests, adopting pre-emptive screening test (admission and/or repeated screening), and providing isolation facilities. Based on the experimentation results, the practical indications to the management of MRSA in the hospital setting can be concluded. These indications may help the hospital to effectively control MRSA.

6.2 Experimental Factors and Model Responses

6.2.1 Experimental Factors

In experimental design terminology, the input parameters and structural assumptions of a model which are to be tested by the model experimentation are called experimental factors, and the output performance measurements are called model responses. The decision as to which parameters and structural assumptions are considered fixed aspects of a model and which are experimental factors depends on the goals of the study (Law 2007). In accordance with the objective of the modelling study, the experimental factors selected are those input parameters or structural assumptions that represent either key intervention policies or key influencing factors of MRSA. Overall, eight experimental factors are chosen and listed in the order of their controllability in Table 6.1. In general, the hospital has more control over

intervention polices than influencing factors. Detailed descriptions of these experimental factors are given in Section 3.8.1 and 3.8.2.

The base/alternative values of each experimental factor are also given in Table 6.1 and they will be used for the fractional factorial design. The base value attempts to reflect the less favourable condition for preventing and controlling MRSA, while the alternative value attempts to represents a realistic value under improved conditions.

Table 6.1 Experimental factors and their base/alternative values

Category	Experimental factor	Factor index	Base value (-)	Alternative value (+)
Controllable	Test turnaround time (days)	1	4	1
	Screening strategy	2	Admission only	Admission plus 4 day repeat screening
	Number of Isolation beds (beds)	3	0	6
Less controllable	*k*: effectiveness of decolonisation treatment	4	0.5	0.1
	C: transmission coefficient	5	0.15	0.1
	m: proportion of transmission within bay	6	0.1	0.9
	Average length of stay (days)	7	6[1]	4[2]
Uncontrollable	Endemic setting (%)	8	10%	2%

1: In the test ward model, the length of stay for non-primary case patients will be sampled from the gamma distribution with shape parameter 1.2 and scale parameter 5.
2: In the test ward model, the length of stay for non-primary case patients will be sampled from the gamma distribution with shape parameter 1.2 and scale parameter 3.333.

Test Turnaround Time (TTT)

The factor of test turnaround time represents an important intervention policy of adopting a rapid screening test. The factor is highly controllable since the hospital can decide which screening test (with different test turnaround time) is adopted. The base and alterative values of the factor are 4 days and 1 day respectively.

Screening Strategy (SS)

Screening strategy represents another important intervention policy and it is also a much controllable factor. The base screening strategy is "Admission only" which means only admission screening is performed. The alternative strategy is "Admission plus 4 day repeat screening" which means both admission screening and four day repeat screening are implemented.

Number of Isolation Beds (IB)

The number of isolation beds is also under the control of the hospital and it reflects the intervention policy of isolating identified MRSA patients. The base scenario is that there are no isolation beds and the alternative scenario is that six isolation beds are provided.

Two issues need to be taken into consideration when analysing the effectiveness of this experimental factor. Firstly, the isolation beds in the ward are not solely devoted to MRSA colonised patients (e.g., patients with other infectious diseases may be isolated). Actually, the parameter of the availability of the isolation bed (i.e., the probability that an isolation bed may not be used to isolate MRSA patient due to the reason that it is occupied for other reasons) is included in the model to represent this situation. Secondly, since the patient arrival rate is fixed at its default value across all experimentations, a change of the number of isolation beds may actually change the ward occupancy since the product of the average length of stay and patient arrival rate should always equal to the product of the number of beds in the ward and the average ward occupancy (see Equation 6.1). When the average length of stay and patient arrival rate are fixed, the more isolation beds are introduced, the lower the average ward occupancy is.

$$\textit{(Average Length of Stay)} \times \textit{(Patient Arrival Rate)} = \textit{(Number of Beds in Ward)} \times \textit{(Average Ward Occupancy)} \quad (6.1)$$

Other Experimental Factors

Other less controllable experimental factors include the effectiveness of decolonisation treatment (EDT), the transmission coefficient (TC), the proportion of transmission coming from within the same bay (PWB), the length of stay (LOS), and the endemic setting (ES). Their base and alternative values are given in Table 6.1.

6.2.2 Model Responses

The model responses for the experimentation are the absolute number of secondary cases and the transmission ratio which is the ratio of the number of secondary cases to

the number of primary cases. These two model responses are used to measure the effectiveness and robustness of various MRSA intervention policies.

6.3 Experimental Design Methods

When the arduous process of building, verifying and validating a simulation model is completed, it is time to have the model work for you; and one extremely effective way of accomplishing this task is to apply experimental design methods to help explore the model (Sanchez 2007). In this study, two formal experimental design methods are adopted: fractional factorial design and response surface design.

6.3.1 Fractional Factorial Design

The most commonly applied experimental design method appears to be full 2^k factorial design. According to the method, all k experimental factors will be set at two levels (i.e., the base level and the alternative level), and a full combination of the k experimental factors with two levels will result 2^k design points in total. Normally multiple replication runs are performed at each design point, and mean model responses are estimated. Standard statistical techniques exist to analyse the responses and calculate the main effect of each experimental factor as well as arbitrary higher-order interaction effects among the factors.

The main effect of each experimental factor measures the average change of the model response due to a change of the factor value from its base to the alternative level, considering all possible combinations of the other factors. In this study, the main effect of each experimental factor indicates the average effectiveness of the intervention policy or the average sensitivity of the influencing factor, considering all possible combinations of the rest of the experimental factors. The two-way interaction effect measures the level of interactions between two factors, i.e., the effect of one factor depends in some way on the level of the other factor. The two-way interaction effect between factor i and factor j is the difference between the average effect of factor i when factor j is at its base level and the average effect of factor i when factor j is at its alternative value. In this study, the two-way interaction effect may disclose the potential dependency between pairs of experimental factors.

Given a limited number of experimental factors, a full 2^k design has relatively few design points, is easy to implement, and allows you to examine any higher-order interactions without confounding among factors.

One assumption of the factorial design is that each experimental factor only has two levels tested: base and alternative level. Therefore, it is not possible to explore the factor on more than two levels and linearity is implicitly assumed between the experimental factor and model responses, and between different experimental factors. Another drawback of the method is that when the number of experimental factors increases, the number of total design points increases exponentially and will soon become intractable.

The reason to use the fractional factorial design (with resolution V), rather than a full factorial design, is to reduce the number of design points and subsequently the computational time and effort. A full factorial design with eight experimental factors (the number of experimental factors in this study) needs 256 design points ($2^8 = 256$), each representing a unique combination of the base/alternative levels of all eight factors. Like model validation, for each design point, the simulation model will run 500 replications to estimate the mean model responses; and each simulation run will last 415 days (365 days for data collection preceded by 50 day warm-up period). This implies a total of 128,000 ($256 \times 500 = 128000$) runs are required for a full factorial design experiment. The fractional factorial design can significantly reduce the number of design points; and the resolution V can guarantee that not only main effects but also the two-way interaction effects can be estimated without confounding with each other (Law 2007).

Table 6.2 gives the definition of resolution III, IV, and V in 2^{k-p} fractional factorial design according to Law (2007). Standard techniques exist to construct a 2^{k-p} design matrix and estimate the main and non-confounding two-way interaction effects (if the resolution allows) of the experimental factors (Law 2007).

Table 6.2 Definition of resolution III, IV and V of fractional factorial design (source: Law 2007)

Resolution	Definition
III	No main effect is confounded with any other main effect, but main effects are confounded with two-way interactions and some two-way interactions may be confounded with each other.
IV	No main effect is confounded with any other main effect or with any two-way interaction, but two-way interactions are confounded with each other.
V	No main effect or two-way interaction is confounded with any other main effect or two-way interactions.

With eight experimental factors, fractional factorial design with resolution V needs 64 design points. According to the rules for determining the combinations of experimental factors in each design point, the design matrix is constructed (see the first ten columns of Table 6.4). During model experimentation, the model responses of each design point are estimated based on 500 replications. Since multiple replications are performed for each design point, the model responses may be used not only to estimate the mean main and two-way interaction effects, but also the distribution and confidence interval for each main and two-way interaction effect.

6.3.2 Response Surface Design

Compared to factorial design, response surface design can test the experimental factor on many different levels, so that non-linear and more detailed relationships can be revealed. A response surface design tests two experimental factors at a time while keeping all other experimental factors and input parameters at default values.

If the first experimental factor has n levels and the second factor has m levels to be tested, then the total number of design points for the response surface is the product of n and m (i.e., $n \times m$). For each design point, the model response will be estimated based on 500 replications and a three-dimensional diagram will be constructed to show the response surface with the two horizontal axes representing the levels of the two experimental factors and the vertical axis representing the corresponding mean model responses. The detailed and potential non-linear relationships between each of the two experimental factors and the model response and the potential non-linear interaction between the two experimental factors can be captured by the response surface.

The drawback of response surface design is that it needs a large number of design points, especially if more levels of each factor are tested. Another drawback of the design is that it only tests two factors at a time while the values of other potential experimental factors need to be fixed. This assumption means response surface design can not reveal the potential interactions between the two factors tested and other experimental factors.

Following the fractional factorial design, the response surface design will be carried out on those pairs of experimental factors that both demonstrate significant two-way interaction effects in the factorial design and have potential practical implications on MRSA control and prevention. Experimental design itself is a vast research area in the operational research and statistics domain. Detailed discussion of experimental design methods (including factorial design, response surface design and other experimental design methods) can be found in the relevant subject literature (Chapter 9 of Kleijnen and Groenendaal 1992; Kleijnen *et al.* 2005; Chapter 12 of Law 2007).

6.4 Test Ward Configuration

A hypothetical test ward, or a benchmark scenario, that represents the typical characteristics of all scenarios of the MRSA case study is created and its default input values are determined. As a principle, if an input parameter has the same value across all fourteen validation scenarios, then the same value will be used for the test ward as well. Otherwise, the input value will be re-estimated based on the pooled observed data from all scenarios.

Ward Layout

The test ward represents a typical study ward from the research project and should also be representative as a typical surgical ward in the UK hospital. It is assumed that, by default, the test ward consists of 34 beds, among which four are isolation beds. The remaining 30 beds are distributed evenly in five ward bays (e.g., each ward bay has six beds).

Screening Test

The test ward carries out either admission screening or four day repeat screening. Regarding the turnaround time of the screening test, since no specific test method (e.g., conventional culture or rapid PCR test) is assumed to be applied to the test ward, an average value of two days is used.

Decolonisation Treatment

The duration and success rate of decolonisation treatment are set at five days and 74.6% respectively in the test ward as both values are shared by all validation scenarios. Like the validation models, the test ward also assumes that successful treatment needs to be confirmed by three successive weekly negative screening tests. As to the delay of decolonisation treatment after the detection of MRSA, an average delay of 0.77 day was estimated from the pooled observed data.

Vulnerability of Susceptible Patients

It is assumed that susceptible patients in the test ward have the same level of vulnerability which complies with the average vulnerability of patients in the research project.

Length of Stay

In the validation models, the patient's length of stay is sampled from empirical distributions. For the test ward, the use of parametric distributions is more appropriate since it is easier to manipulate the mean and the shape of the length of stay by adjusting the parameter values of the chosen distribution. The use of parametric distributions can also help other researchers to replicate the model experiments.

Like the validation models, the length of stay in the test ward is classified into two categories: one for primary case patients and the other for non-primary case patients (see Section 5.2.1). The majority of patients are non-primary case patients, i.e., patients who are not colonised with MRSA on admission. The parametric distribution for the length of stay of non-primary case patients will be determined first. Due to the limited number of primary case patients, it is difficult to fit a separate parametric distribution. Instead, the lengths of stay of primary case patients are determined by multiplying the length of stay distribution of non-primary case patients and the ratio

of the average length of stay of the primary case patients to the non-primary case patients.

Based on 13,417 observed lengths of stay, the parametric distribution for non-primary case patients selected by the distribution fitting package, Bestfit®, is a gamma distribution with the shape parameter, α, equal to 1.2, and the scale parameter, β, equal to 5.243. According to the property of the gamma distribution, the mean length of stay equals the product of α and β, which is 6.291 days. The Chi-square test is also satisfied ($p<0.005$). Figure 6.1 illustrates the comparison between the fitted gamma distribution and the histogram of the observed lengths of stay of non-primary case patients. Regarding the lengths of stay of primary case patients, a multiplying factor of 1.639, which is the ratio of average length of stay of primary case patients (i.e., 10.311 days) to the average length of stay of non-primary case patients (i.e., 6.291 days), is estimated from the observed data.

When the average length of stay needs to be changed during experimentation, the shape parameter, α, will keep the same value and the scale parameter, β, will be adjusted so that the product α and β equals the desired mean length of stay.

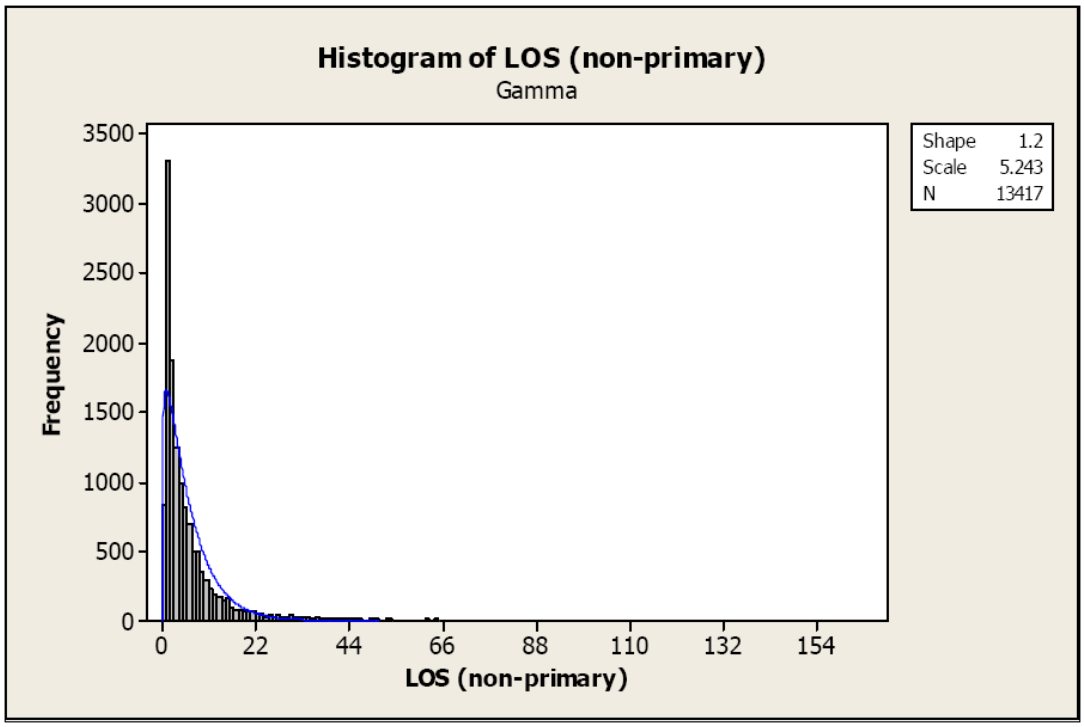

Figure 6.1 Comparison between the fitted gamma distribution and the observed lengths of stay of non-primary case patients

Other Input Parameters

The default input parameter values of the arrival rate, the endemic setting and the availability of isolation beds are all estimated directly from the observed data. The average patient arrival rate during the study period is 4.7 patients per day. The endemic setting and the availability of isolation beds are 3.4% and 19.8% respectively. For the input parameters m (i.e., the proportion of transmission risk coming from within the same bay compared to the whole ward), k (i.e., the effectiveness of decolonisation treatment) and s (i.e., the inter-bay movement rate), the test ward adopts the same assumptions as the validation models which are 0.667, 0.4 and 0.1 respectively. The transmission coefficient of the test ward uses the weighted mean transmission coefficient estimated based on 13 scenarios which is 0.1414 (see Section 5.3.3). Table 6.3 summarises the default input parameter values of the test ward.

Table 6.3 Default input parameter values for the test ward

Category	Parameter	Symbol	Value
Ward layout	Total beds in the ward (beds)		34
	Isolation beds in the ward (beds)		4
	Beds in bay1 (beds)		6
	Beds in bay2 (beds)		6
	Beds in bay3 (beds)		6
	Beds in bay4 (beds)		6
	Beds in bay5 (beds)		6
Screening test	Test turnaround time (days)		2
	Repeat screening interval (days)		4
Decolonisation treatment	Delay of decolonisation treatment (days)		0.77
	Decolonisation treatment duration (days)		5
	Decolonisation treatment success rate		74.7%
Length of stay	Length of stay distribution for non-primary case patients (days)		Gamma(1.2, 5.243)
	Non-primary case patients mean length of stay (days)		6.291
	Multiplying factor for primary case patients length of stay		1.639
	Primary case patients mean length of stay (days)		10.311
	All patients mean length of stay (days)		6.404
Other information	Patient arrival rate		4.7
	Endemic setting		3.4%
	Availability of isolation beds		19.8%
Other model assumptions	Transmission coefficient	C	0.1414
	Proportion of risk within bay	m	0.667
	Effectiveness of decolonisation treatment	k	0.4
	Inter-bay movement rate	s	0.1

6.5 Model Experimentation: Fractional Factorial Design

6.5.1 Experimental Results

Model Responses

For each of the 64 design points, the eight selected experimental factors will take either the base or alternative value according to the design matrix given in Table 6.4. For example, at the first design point (the third row of Table 6.4), the first six experimental factors will take their base values while the last two experimental factors will take the alternative values. All other input parameters of the test ward are set at default values given in Table 6.3. Once a design point is configured, the model will

run for 500 replications, each lasts for 415 days (365 days for data collection and 50 days for warm-up period), and the mean number of primary and secondary cases, and mean transmission ratio are shown in the last three columns of Table 6.4. These model responses will be used to estimate the main and two-way interaction effects of the experimental factors.

Table 6.4 Fractional factorial design matrix and model experimentation results based on 500 replications

Design point	Factor 1	2	3	4	5	6	7	8	Mean primary Cases	Mean secondary Cases	Mean transmission Ratio
	TTT	SS	IB	EDT	TC	PWB	LOS	ES			
1	-	-	-	-	-	-	+	+	34.5	40.9	1.189
2	+	-	-	-	-	-	-	-	168.3	212.0	1.263
3	-	+	-	-	-	-	-	-	168.2	214.5	1.279
4	+	+	-	-	-	-	+	+	34.2	27.2	0.797
5	-	-	+	-	-	-	-	+	34.5	79.3	2.330
6	+	-	+	-	-	-	+	-	172.3	117.3	0.682
7	-	+	+	-	-	-	+	-	171.8	139.8	0.815
8	+	+	+	-	-	-	-	+	34.2	36.7	1.077
9	-	-	-	+	-	-	-	+	34.1	65.9	1.937
10	+	-	-	+	-	-	+	-	171.8	89.3	0.520
11	-	+	-	+	-	-	+	-	172.1	123.4	0.718
12	+	+	-	+	-	-	-	+	34.0	21.4	0.631
13	-	-	+	+	-	-	+	+	34.0	33.3	0.981
14	+	-	+	+	-	-	-	-	172.4	147.1	0.854
15	-	+	+	+	-	-	-	-	170.9	164.6	0.965
16	+	+	+	+	-	-	+	+	34.1	16.9	0.497
17	-	-	-	-	+	-	+	-	172.4	91.1	0.530
18	+	-	-	-	+	-	-	+	34.4	27.1	0.787
19	-	+	-	-	+	-	-	+	34.1	30.6	0.900
20	+	+	-	-	+	-	+	-	170.4	66.0	0.388
21	-	-	+	-	+	-	-	-	172.3	134.2	0.780
22	+	-	+	-	+	-	+	+	34.3	16.3	0.475
23	-	+	+	-	+	-	+	+	34.5	20.8	0.604
24	+	+	+	-	+	-	-	-	171.3	86.6	0.506
25	-	-	-	+	+	-	-	-	167.6	112.3	0.672
26	+	-	-	+	+	-	+	+	34.1	12.3	0.363
27	-	+	-	+	+	-	+	+	33.5	17.5	0.526
28	+	+	-	+	+	-	-	-	167.8	53.5	0.319
29	-	-	+	+	+	-	+	-	171.1	75.8	0.444
30	+	-	+	+	+	-	-	+	34.1	16.7	0.489
31	-	+	+	+	+	-	-	+	34.0	22.7	0.669
32	+	+	+	+	+	-	+	-	171.1	44.3	0.259
33	-	-	-	-	-	+	+	-	171.9	141.0	0.822
34	+	-	-	-	-	+	-	+	33.9	48.8	1.444

35	-	+	-	-	-	+	-	+	34.7	52.8	1.523
36	+	+	-	-	-	+	+	-	171.5	102.8	0.600
37	-	-	+	-	-	+	-	-	171.6	181.4	1.059
38	+	-	+	-	-	+	+	+	34.1	17.4	0.510
39	-	+	+	-	-	+	+	+	34.4	26.0	0.762
40	+	+	+	-	-	+	-	-	171.2	111.7	0.652
41	-	-	-	+	-	+	-	-	168.5	184.3	1.097
42	+	-	-	+	-	+	+	+	34.5	20.8	0.607
43	-	+	-	+	-	+	+	+	34.2	28.4	0.833
44	+	+	-	+	-	+	-	-	168.6	82.1	0.487
45	-	-	+	+	-	+	+	-	171.3	94.8	0.554
46	+	-	+	+	-	+	-	+	34.1	26.1	0.767
47	-	+	+	+	-	+	-	+	33.9	34.2	1.008
48	+	+	+	+	-	+	+	-	171.7	56.2	0.327
49	-	-	-	-	+	+	+	+	34.4	20.6	0.597
50	+	-	-	-	+	+	-	-	169.4	99.0	0.585
51	-	+	-	-	+	+	-	-	169.0	113.7	0.674
52	+	+	-	-	+	+	+	+	34.0	14.6	0.428
53	-	-	+	-	+	+	-	+	34.2	25.2	0.739
54	+	-	+	-	+	+	+	-	171.2	47.0	0.275
55	-	+	+	-	+	+	+	-	171.0	62.4	0.365
56	+	+	+	-	+	+	-	+	34.4	13.4	0.391
57	-	-	-	+	+	+	-	+	34.2	26.1	0.765
58	+	-	-	+	+	+	+	-	170.9	48.4	0.284
59	-	+	-	+	+	+	+	-	170.9	70.8	0.415
60	+	+	-	+	+	+	-	+	34.2	11.6	0.339
61	-	-	+	+	+	+	+	+	34.2	15.7	0.459
62	+	-	+	+	+	+	-	-	171.3	57.3	0.334
63	-	+	+	+	+	+	-	-	170.4	81.6	0.480
64	+	+	+	+	+	+	+	+	34.4	8.1	0.236

Average Main and Two-way Interaction Effects

The average main and two-way interaction effects are calculated using standard techniques (Law 2007) based on the mean transmission ratios of each design point. The average main effects of the factors are listed in the last row of Table 6.5; while the average two-way interaction effects are given in the cells where the two factors intercept in the table. Since the two-way interaction effect between factors *i* and *j* is the same as the effect between *j* and *i*, only half of the cells in the table are filled. Detailed analyses of the effects are discussed in Section 6.5.2 and 6.5.3.

Table 6.5 Main and two-way interaction effects of fractional factorial design

		Factor 1	2	3	4	5	6	7	8
		TTT	SS	IB	EDT	TC	PWB	LOS	ES
Factor 1	TTT	x							
2	SS	0.004	x						
3	IB	-0.002	0.015	x					
4	EDT	-0.034	-0.004	0.019	x				
5	TC	0.094	0.080	0.026	0.064	x			
6	PWB	0.048	0.062	-0.068	0.035	0.067	x		
7	LOS	0.081	0.103	0.007	0.074	0.137	0.044	x	
8	ES	-0.083	-0.054	-0.012	-0.028	-0.086	-0.027	-0.060	x
Main effect		**-0.291**	**-0.148**	**-0.093**	**-0.187**	**-0.422**	**-0.151**	**-0.311**	**0.177**

Distributions of each Main and Two-way Interaction Effects

For one replication of every design point (i.e., 64 simulation runs from 64 design points), one set of the estimates of the main and two-way interaction effects can be obtained. Since each design point has 500 replications, each main and two-way interaction effect will have 500 different estimates. Apart from the average effects which are given in Table 6.5, in order to examine the variation of each main and two-way interaction effect, confidence intervals and other descriptive statistics (e.g., range, first and third quartiles, percentage of negative effects) are calculated based on these individual estimates of each effect (see Table 6.6).

The 95% confidence intervals of each main and two-way interaction effect are shown in the third (lower bound) and fourth (upper bound) columns of the table. The confidence interval will be highlighted if zero is not included in the interval (i.e., the effect is statistically significant and different from zero, either positive or negative). The first and third quartiles and the overall range (i.e., minimum and maximum individual estimates) of each effect based on 500 individual estimates are also given in the table (from fifth to eighth column), and are highlighted if the interval does not contain zero (i.e., all individual effects between first and third quartiles are different from zero, or all individual effects are different from zero, either positive or negative). The last column of the table shows the percentage of individual effects that falls below zero, and the value will be highlighted if either 90% of individual effects are all positive (i.e., the value is less than 10%) or negative (i.e., the value is more than 90%) which both indicates a significant effect.

Table 6.6 Confidence interval and descriptive statistics of the main and two-way interactive effects

Effects	Mean effect	Confidence interval (95%)		First and third quartile		Range		Percentage below zero
		Lower	Upper	First	Third	Min	Max	
1	-0.291	**-0.296**	**-0.286**	**-0.327**	**-0.258**	**-0.451**	**-0.132**	**100.0%**
2	-0.148	**-0.152**	**-0.143**	**-0.186**	**-0.109**	**-0.337**	**-0.016**	**100.0%**
3	-0.093	**-0.098**	**-0.088**	**-0.128**	**-0.055**	-0.274	0.061	**94.6%**
4	-0.187	**-0.192**	**-0.182**	**-0.228**	**-0.149**	-0.358	0.009	**99.8%**
5	-0.422	**-0.427**	**-0.417**	**-0.458**	**-0.384**	**-0.590**	**-0.255**	**100.0%**
6	-0.151	**-0.156**	**-0.146**	**-0.189**	**-0.114**	-0.324	0.005	**99.6%**
7	-0.311	**-0.316**	**-0.305**	**-0.346**	**-0.271**	**-0.498**	**-0.122**	**100.0%**
8	0.177	**0.172**	**0.182**	**0.135**	**0.216**	**0.014**	**0.405**	**0.0%**
1x2	0.004	-0.001	0.008	-0.034	0.039	-0.165	0.235	46.0%
1x3	-0.001	-0.006	0.003	-0.040	0.036	-0.168	0.175	50.0%
1x4	-0.034	**-0.040**	**-0.029**	-0.072	0.007	-0.196	0.147	71.2%
1x5	0.094	**0.089**	**0.099**	**0.057**	**0.131**	-0.069	0.287	**4.6%**
1x6	0.048	**0.043**	**0.053**	**0.011**	**0.086**	-0.151	0.232	20.0%
1x7	0.081	**0.076**	**0.086**	**0.042**	**0.117**	-0.085	0.244	**6.8%**
1x8	-0.083	**-0.088**	**-0.078**	**-0.120**	**-0.046**	-0.287	0.104	**92.6%**
2x3	0.015	**0.010**	**0.020**	-0.024	0.054	-0.189	0.179	41.8%
2x4	-0.004	-0.009	0.002	-0.043	0.034	-0.163	0.183	53.4%
2x5	0.080	**0.075**	**0.085**	**0.040**	**0.120**	-0.056	0.256	**8.0%**
2x6	0.062	**0.057**	**0.066**	**0.023**	**0.099**	-0.116	0.267	13.0%
2x7	0.102	**0.097**	**0.108**	**0.064**	**0.140**	-0.043	0.290	**4.8%**
2x8	-0.054	**-0.059**	**-0.048**	**-0.090**	**-0.010**	-0.255	0.103	82.2%
3x4	0.019	**0.013**	**0.024**	-0.018	0.059	-0.162	0.170	36.2%
3x5	0.026	**0.021**	**0.032**	-0.011	0.067	-0.164	0.232	32.0%
3x6	-0.068	**-0.074**	**-0.063**	**-0.106**	**-0.027**	-0.291	0.142	88.2%
3x7	0.007	**0.002**	**0.012**	-0.032	0.046	-0.136	0.161	44.8%
3x8	-0.012	**-0.017**	**-0.006**	-0.048	0.029	-0.193	0.167	56.4%
4x5	0.064	**0.059**	**0.069**	**0.026**	**0.099**	-0.102	0.248	11.8%
4x6	0.035	**0.030**	**0.040**	-0.003	0.076	-0.156	0.262	28.0%
4x7	0.074	**0.069**	**0.079**	**0.034**	**0.109**	-0.105	0.265	10.6%
4x8	-0.028	**-0.033**	**-0.023**	-0.067	0.009	-0.203	0.164	68.2%
5x6	0.067	**0.062**	**0.072**	**0.034**	**0.103**	-0.097	0.277	11.6%
5x7	0.137	**0.132**	**0.142**	**0.100**	**0.173**	-0.044	0.299	**0.8%**
5x8	-0.086	**-0.091**	**-0.081**	**-0.123**	**-0.047**	-0.276	0.093	**94.4%**
6x7	0.044	**0.038**	**0.049**	**0.000**	**0.085**	-0.102	0.207	25.0%
6x8	-0.027	**-0.032**	**-0.022**	-0.065	0.009	-0.188	0.128	69.4%
7x8	-0.060	**-0.065**	**-0.055**	**-0.098**	**-0.020**	-0.257	0.132	84.2%

The range and confidence interval (with confidence level of 95%) of each main and two-way interaction effect are shown in Figure 6.2; while the range and the first and third quartiles of each main and two-way interaction effect are shown in Figure 6.3. In the diagrams, the vertical thin line represents the range of 500 individual estimates of

the effects while the rectangular box indicates the 95% confidence interval or the first and third quartiles.

Due to the large sample size (i.e., 500), it is easy to conclude that the average main and two-way interaction effects are statistically significant (i.e., zero is not included in the confidence interval). As Table 6.6 shows, 33 out of 36 main and interaction effects are statistically significant from zero. However, the confidence interval only focuses on the interval within which the 'true' mean is likely to lie, rather than the extent of the dispersion or variation of individual estimates. In the context of investigating the effectiveness of MRSA intervention policies, the distribution and variation of individual effects are probably more important to the understanding of the impact of experimental factors on transmission dynamics. For example, for the two-way interaction effect between factors 2 and 3, although the confidence interval shows the main effect is statistically significant and positive (0.01 to 0.02), a big proportion of individual effects (41.8%) are actually negative and zero is within the first and third quartiles (-0.024 to 0.054). To illustrate the different pictures presented by quartiles and ranges, 24 out of 36 intervals of first and third quartiles do not contain zero (i.e., effects are significantly positive or negative), and only 5 out of 36 effects are all positive or negative across the whole range (i.e., effect are significantly positive or negative even in extreme cases); and for 15 out of 36 effects, more than 90% of individual effects are either positive or negative (see Table 6.6, and Figure 6.3).

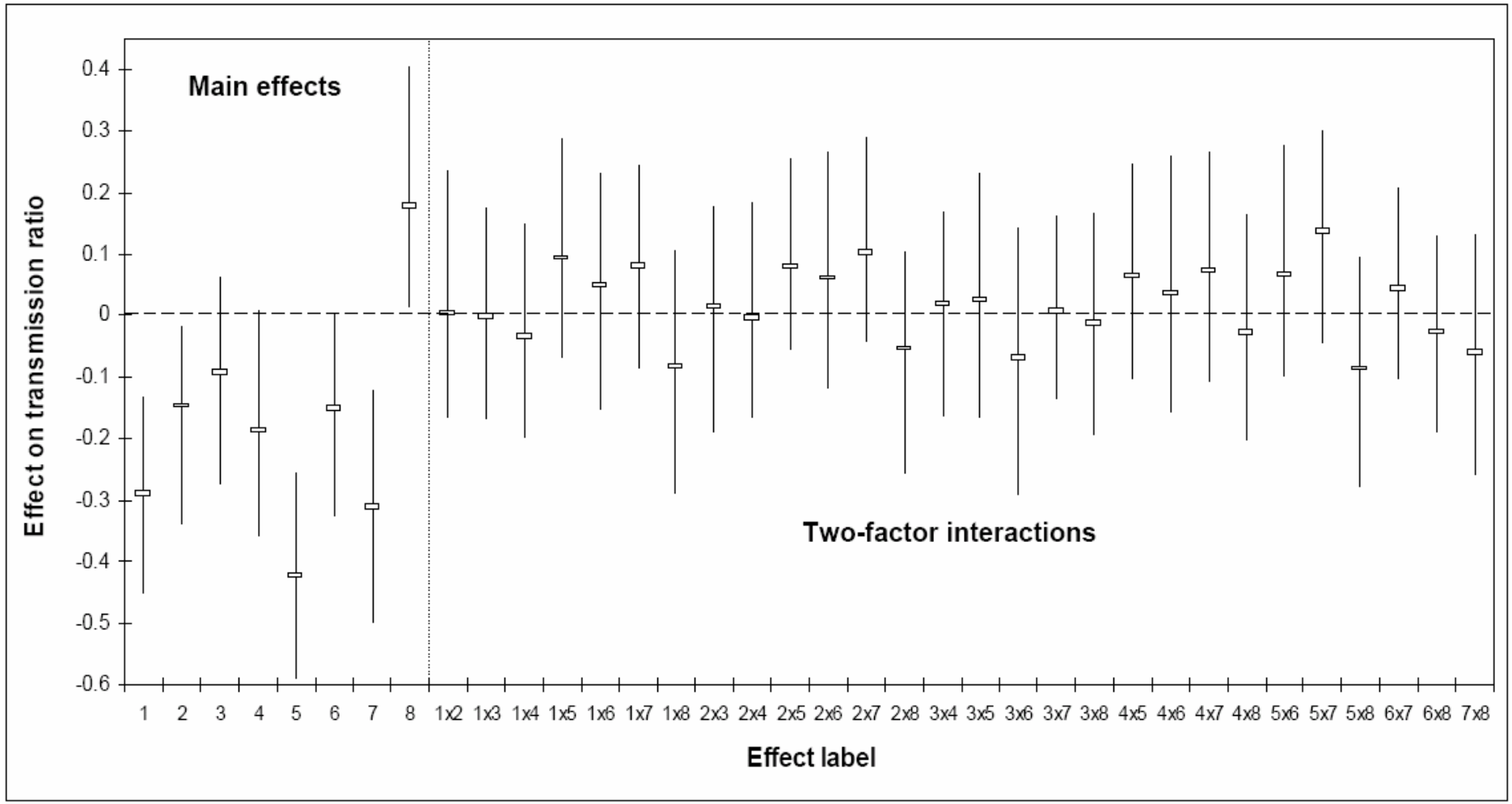

Figure 6.2 Confidence interval and range of the main and two-way interaction effects

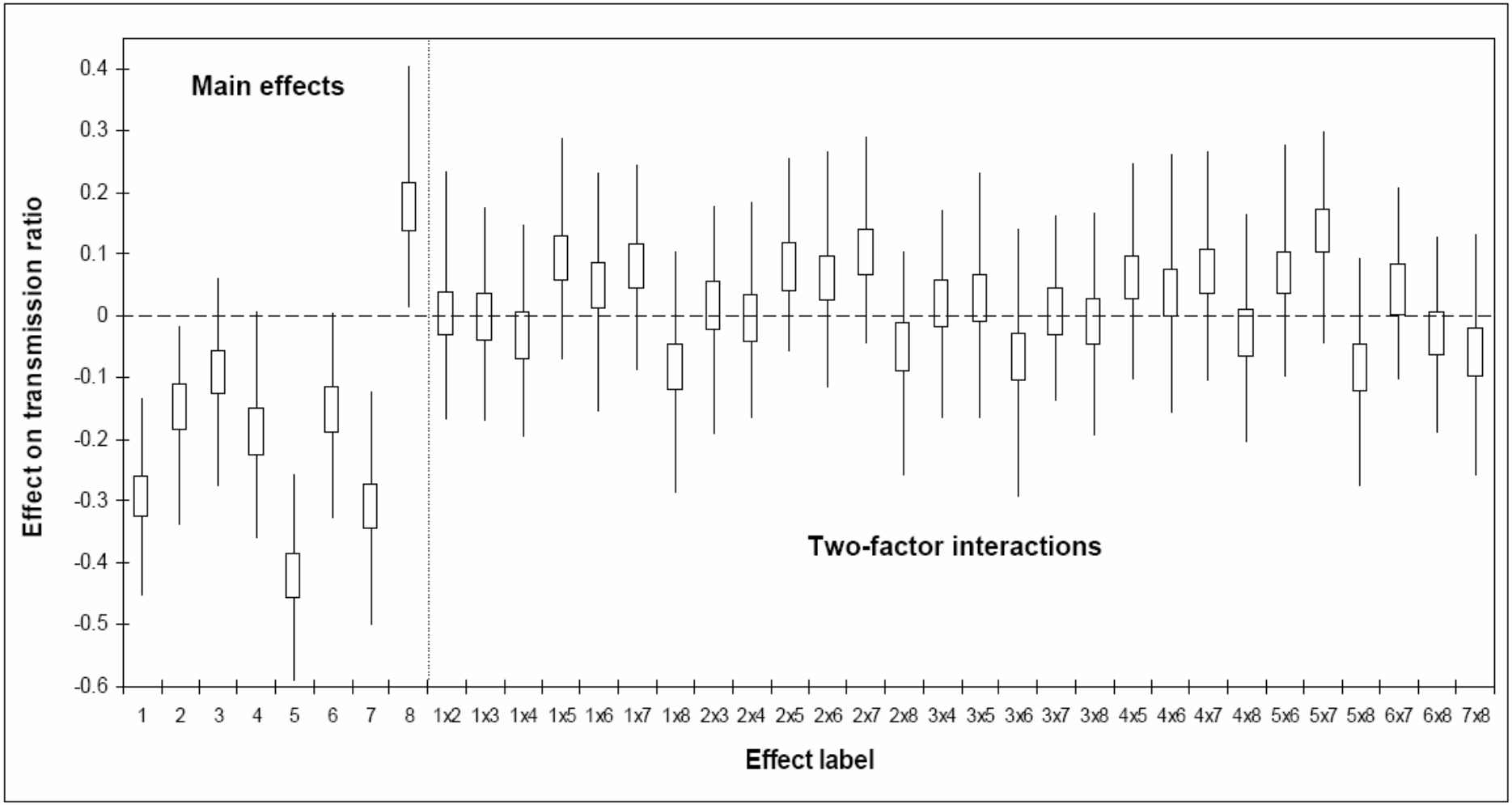

Figure 6.3 First and third quartiles and range of the main and two-way interaction effects

6.5.2 Analysis of Main Effects

The average main effects of the eight experimental factors range from 0.093 (number of isolation beds) to 0.422 (transmission coefficient). Among the eight mean main effects, one is positive (i.e., the endemic setting) and the rest are negative. A positive mean main effect indicates that the average transmission ratio will increase when the experimental factor changes from the base to the alternative value; a negative mean main effect indicates that the average transmission ratio will be reduced when the factor changes from the base to the alternative value. The larger the value of the effect, the more significant of impact on the transmission ratio.

All mean main effects are statistically significant. When considering the distributions of individual effects, for all eight experimental factors, more than 90% of the 500 individual estimates of the effect are either positive (for the factor of endemic setting) or negative (for other experimental factors) which indicates that all main effects are consistent and robust when chance effects are considered. Notably, for five out of eight main effects, all 500 simulated individual effects are either below zero (for the factors of the screening strategy, test turnaround time, transmission coefficient and average length of stay) or above zero (for endemic setting) which implies that even in extreme circumstances, the effects of these experimental factors are robust and consistent.

Transmission Coefficient

The transmission coefficient has the most significant main effect among all experimental factors. Figure 6.4 shows that when the transmission coefficient is set at its base value of 0.15, the average transmission ratio is 0.925, considering all combinations of the other seven factors; while the average transmission ratio is reduced to 0.502 when the transmission coefficient is set at its alternative value of 0.10. The average main effect is therefore -0.422 since the transmission ratio is decreased by 0.422 when the transmission coefficient changes from the base to the alternative value, considering all combinations of other factors.

As the most significant main effect, not only the mean effect is statistically significant (95% confidence interval from -0.427 to -0.417), but also all 500 individual estimates are negative and range from -0.59 to -0.255. Overall, the negative main effect of the

transmission coefficient is very strong and consistent, and the transmission coefficient is the most sensitive influencing factor of MRSA transmission (i.e., a small change to the transmission coefficient will cause a significant change in MRSA transmission).

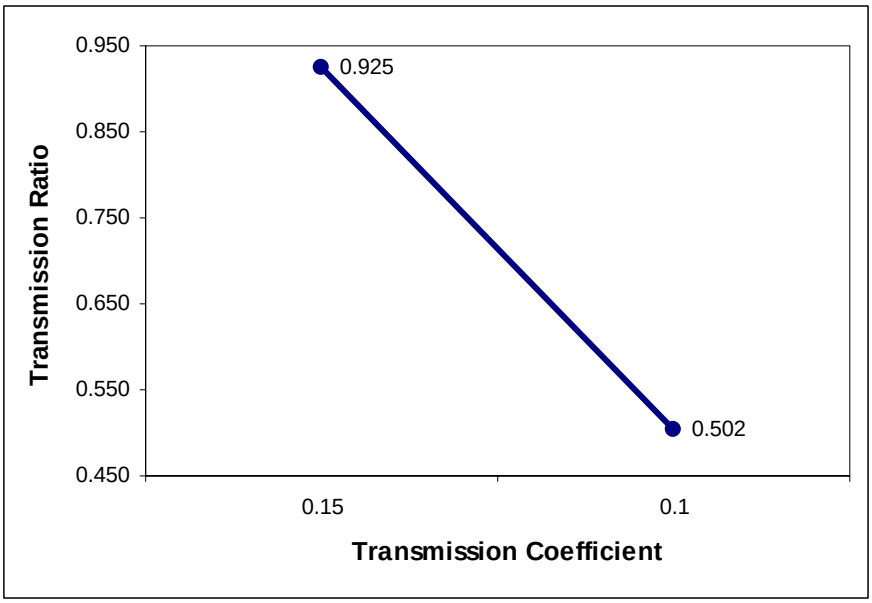

Figure 6.4 Main effect of the transmission coefficient

The practical implication of the main effect is that any measures that can potentially reduce the transmission coefficient of MRSA will be highly effective in reducing MRSA transmission. The measures that may potentially reduce transmission coefficient include enforced hand-washing compliance by the HCWs and visitors, thorough ward cleaning and hygiene and other measures that have not been explicitly represented by the model but may reduce the transmission coefficient. However, as an influencing factor, the transmission coefficient is mainly determined by the type and the strain of the infectious disease and the general vulnerability and risk factors of the patients and may not be fully controlled by the hospital.

The implication to the modelling of MRSA is that the choice of the value of the transmission coefficient as a model input will significantly affect the transmission dynamics. Therefore, great attention must be taken when choosing the parameter value. The experimental result also warrants the calibration of the transmission coefficient from observed data in Chapter 5, since it is possibly the best way to obtain a reasonable estimate of the parameter.

Length of Stay

The average length of stay has the second most significant main effect. On average, the transmission ratio is reduced by 0.311 (from 0.869 to 0.558) when the mean length of stay is reduced from six to four days, considering all combinations of other experimental factors (see Figure 6.5). The negative mean main effect is not only statistically significant (95% confidence interval from -0.316 to -0.305) but also 100% of all 500 individual estimates are negative (range from -0.498 to -0.122). Overall, the main effect is strong and consistent, and the length of stay is a very sensitive influencing factor of MRSA transmission.

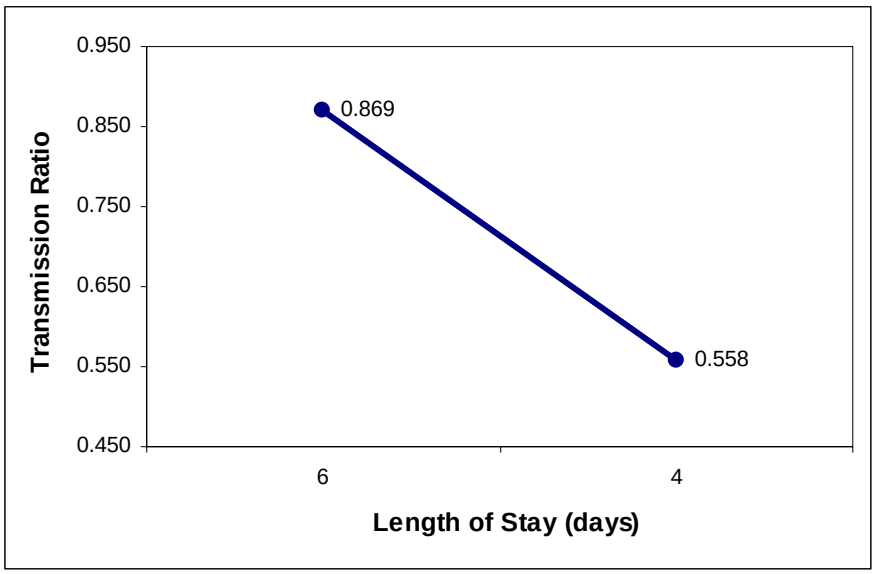

Figure 6.5 Main effect of the length of stay

The negative main effect of the length of stay implies that MRSA transmission can be reduced if the patients' lengths of stay are shortened. In the short term, the hospital may not generally reduce a patient's length of stay simply due to infection control purpose. However, in the long term, it is possible to reduce the average length of stay in the hospital by applying new drugs and healthcare technologies or by changing hospital policies. As long as the same level of service is maintained, hospitals generally have the intention to reduce length of stay since it can both reduce the healthcare cost and increase the hospital capacity. The experimental result shows that another good 'side effect' of reduced length of stay is the reduction of MRSA transmissions.

The sensitivity of length of stay on MRSA transmission also demonstrates the necessity to represent patients' lengths of stay correctly in the model, since a small difference of lengths of stay may cause a big impact on the transmission of MRSA. As a particular strength of the proposed model, empirical distributions are applied during model validation and fitted parametric distribution is used during model experimentation; and in both cases, the length of stay is modelled separately for primary case patients and non-primary case patients.

Test Turnaround Time

The test turnaround time has the third most significant main effect and it is the most effective intervention policy among three policies tested. On average, the transmission ratio is reduced by 0.291 (from 0.859 to 0.568) when the test turnaround time is shortened from four days to one day, considering all combinations of other experimental factors (see Figure 6.6). The negative mean main effect is statistically significant (95% confidence interval from -0.296 to -0.286) and, furthermore, 100% of all 500 individual estimates of the main effects are negative with a range from -0.451 to -0.132. Overall, the main effect is strong and consistent, and reducing test turnaround time (i.e., introducing rapid screening test) is the single most effective intervention policy to reduce MRSA transmission.

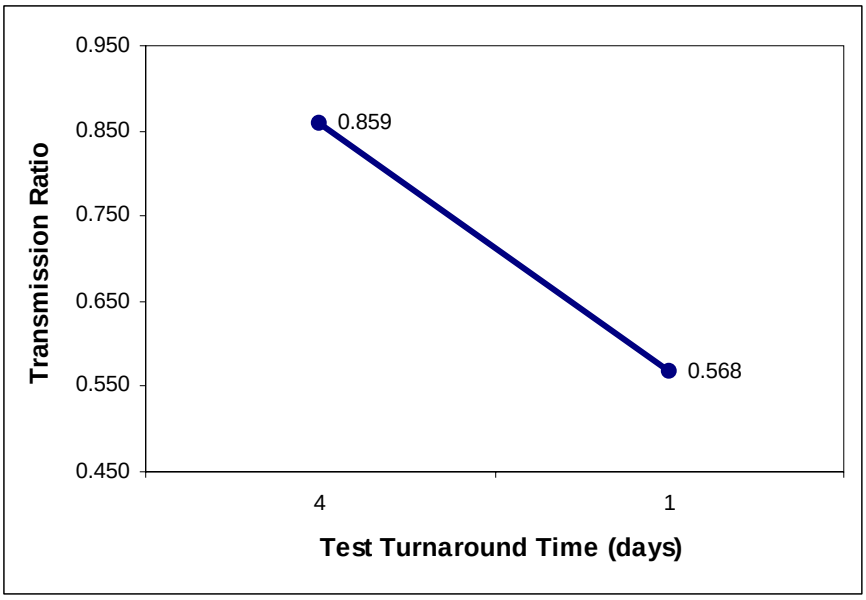

Figure 6.6 Main effect of the test turnaround time

The main effect of the test turnaround time has a clear and practical implication that the adoption of rapid screening test with shorter test turnaround time can significantly reduce MRSA transmission in the hospital setting. Rapid PCR screening tests have been developed in recent years which can provide reliable MRSA results within one day or even shorter. The experimental results show that the rapid test can significantly reduce MRSA transmission. In theory, the hospital should adopt screening test with the shortest possible turnaround time. In reality, the cost factor has to be considered since the rapid screening test is currently more expensive. The hospital may also reduce the test turnaround time by reducing the time spent to transport the samples to and from the laboratory and by reducing the delay in reporting the test results.

Effectiveness of Decolonisation Treatment

The effectiveness of decolonisation treatment has the next most significant main effect (see Figure 6.7). On average, the transmission ratio is reduced by 0.187 (from 0.807 to 0.620) when the effectiveness of the treatment is reduced from 0.5 (i.e., the infectivity of the colonised patient under decolonisation treatment is reduced by 50%) to 0.1 (i.e., the infectivity is reduced by 90%). The mean negative effect is statistically significant (95% confidence interval from -0.192 to -0.182), and a majority of the individual estimates of the effect are negative (99.8% or 499 out of 500 individual estimates). In short, the main effect is strong and consistent, and the effectiveness of decolonisation treatment is a very sensitive influencing factor.

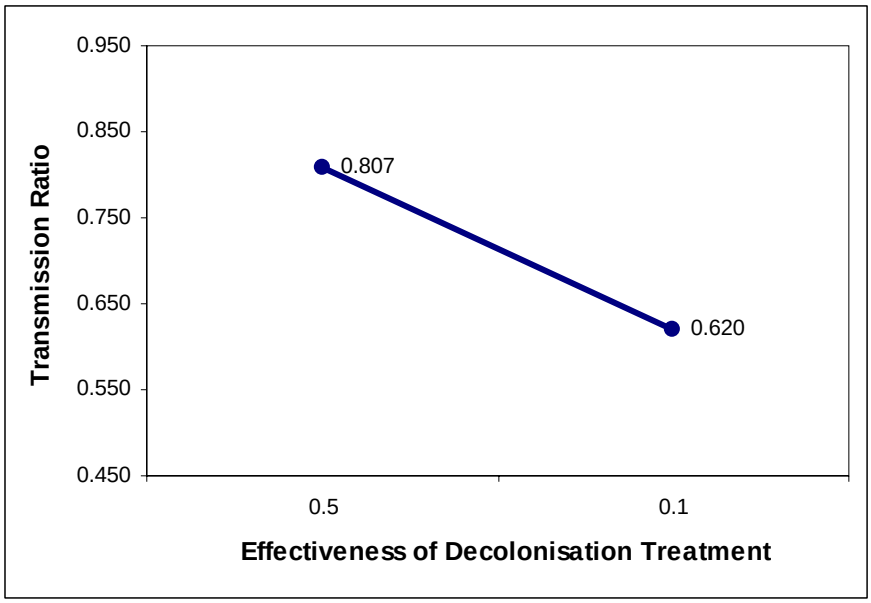

Figure 6.7 Main effect of the effectiveness of the decolonisation treatment

The significant main effect of the effectiveness of decolonisation treatment implies that MRSA transmission can be reduced if the decolonisation treatment can significantly reduce the infectivity of the patient under treatment. The potential methods that may increase the effectiveness of the treatment include adopting new drugs and protocols to treat MRSA patients and enforced barrier precautions for patients under treatment. However, the effectiveness of the treatment is mainly determined by the nature of the treatment itself and it may be difficult to control by the hospital. Attention must also be paid when new antibiotics drugs are used to treat MRSA, since excessive usage of antibiotics may encourage the bacteria to develop even greater antibiotic resistance.

Endemic Setting

The endemic setting, i.e., the proportion of patients colonised with MRSA on admission, also has a significant main effect. On average, the transmission ratio is increased by 0.177 (from 0.625 to 0.802) when the endemic setting is reduced from 10% to 2% (see Figure 6.8). Endemic setting has the only positive main effect among all experimental factors. The positive mean effect is statistically significant (95% confidence interval from 0.172 to 0.182) and all 500 hundred individual estimates are positive. Overall, the positive main effect of the endemic is significant and consistent, and the endemic setting is a sensitive influencing factor of MRSA transmission.

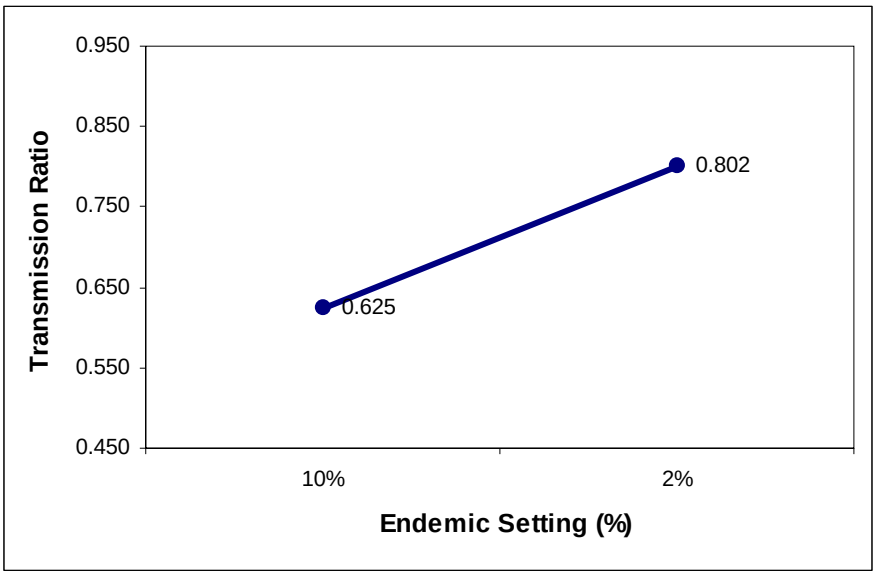

Figure 6.8 Main effect of the endemic setting with transmission ratio as the model response

The model response used for the factorial design is the transmission ratio, which measures the relative ratio of the number of secondary cases to the number of primary cases, rather than the absolute number of secondary cases. When there are similar numbers of primary cases, the two model responses will give the same conclusion. However, when the number of primary cases is different, which is directly related to the endemic setting, the two model responses may provide contradictory conclusions (see Section 3.8.3 for detailed discussion).

Figure 6.9 shows the main effect of the endemic setting using the absolute number of secondary cases, rather than the transmission ratio, as the model response. As expected, the main effect is significantly negative; the average number of secondary cases is reduced sharply by 79 cases (from 106.4 to 27.4) when the endemic setting is reduced from 10% to 2%. Such a significant negative effect is mainly caused by the different number of primary cases associated with different levels of endemic setting.

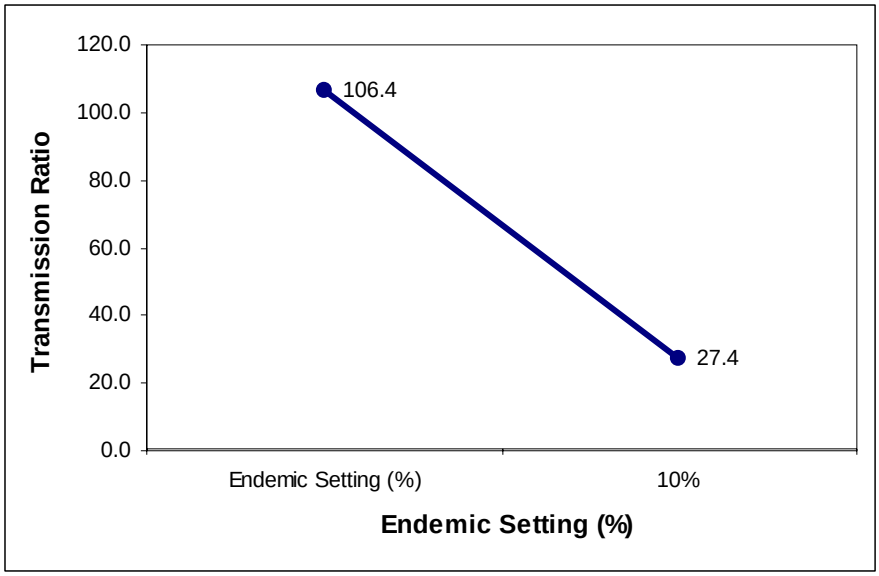

Figure 6.9 Main effect of the endemic setting with the number of secondary cases as the model response

The significant main effect of endemic setting may have limited practical implications since the hospital may not control the factor, especially in the short term. However, if pre-admission screening tests are carried out (i.e., screening patients for MRSA before they are admitted to the hospital), it is possible to reduce the endemic setting by decolonising these patients before their admissions. The main effect of the endemic

setting indicates that, given a fixed total patient population, when fewer colonised patients are admitted to the ward from outside, the average number of secondary cases incurred by one primary case will increase but the total number of secondary cases will decrease sharply.

Proportion of Transmission within Bay

The experimental factor of the proportion of transmission within the ward bay has a significant main effect (see Figure 6.10). On average, the transmission ratio is reduced by 0.151 (from 0.789 to 0.638) when the proportion is increased from 10% (most transmissions come from the whole ward due to global interactions) to 90% (most transmission come from within the same bay due to local interactions). The negative mean main effect is statistically significant (95% confidence level from -0.156 to -0.146) and a majority of individual estimates of the effect are negative (99.6% or 498 out of 500 individual estimates of the effect). Overall, the main effect is strong and consistent, and the proportion of transmission within the ward bay is a sensitive influencing factor of MRSA transmission.

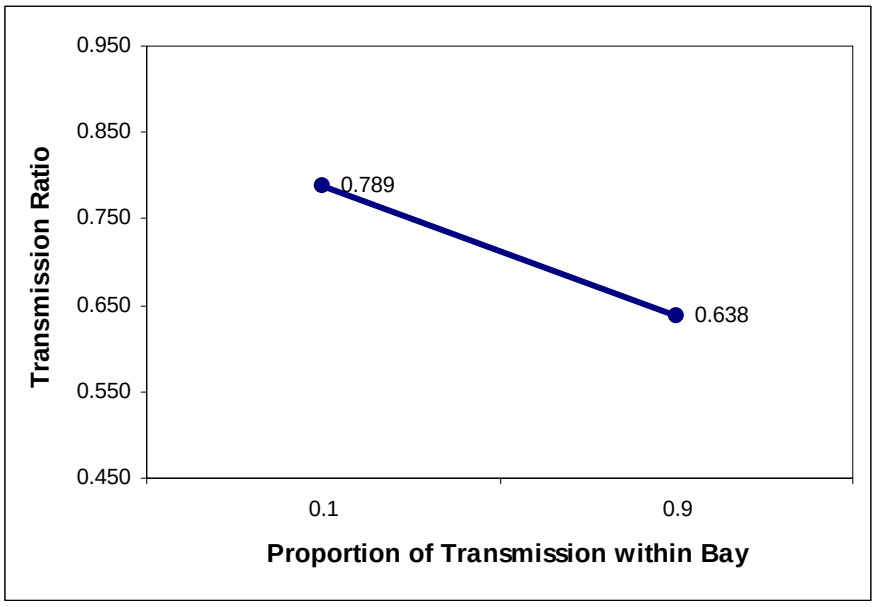

Figure 6.10 Main effect of the proportion of transmission coming from within the same bay

The significant main effect of the proportion of transmission within the bay implies that MRSA transmission can be reduced if a higher proportion of transmission is caused by the local environment within each ward bay rather than the global

environment of the whole ward. If the ward has isolation rooms, the significant effect implies that MRSA transmission can be reduced if the isolation room can be perfectly isolated from the rest of the ward.

The measures that may potentially increase the proportion of transmission within the ward bay include discouraging contacts between patients from different ward bays, physical improvement of ward facilities (e.g., dedicate toilet for each ward bay and isolation room) and strict protocols for isolation. However, the factor is mainly determined by the inherent transmission routes of MRSA and the physical layout of the ward, and is difficult to be totally controlled by the hospital.

Screening Strategy

The screening strategy has a significant main effect and it is the second most effective intervention policy. On average, the transmission ratio is reduced by 0.148 (from 0.787 to 0.64) when the screening strategy changes from admission screening only to admission screening plus four day repeat screening (see Figure 6.11). The negative mean main effect is statistically significant (95% confidence interval from -0.152 to -0.143) and all 500 individual estimates of the effect are negative. Overall, the negative main effect of the screening strategy is strong and consistent, and the introduction of more frequent screening test is an effective intervention policy for reducing MRSA transmission.

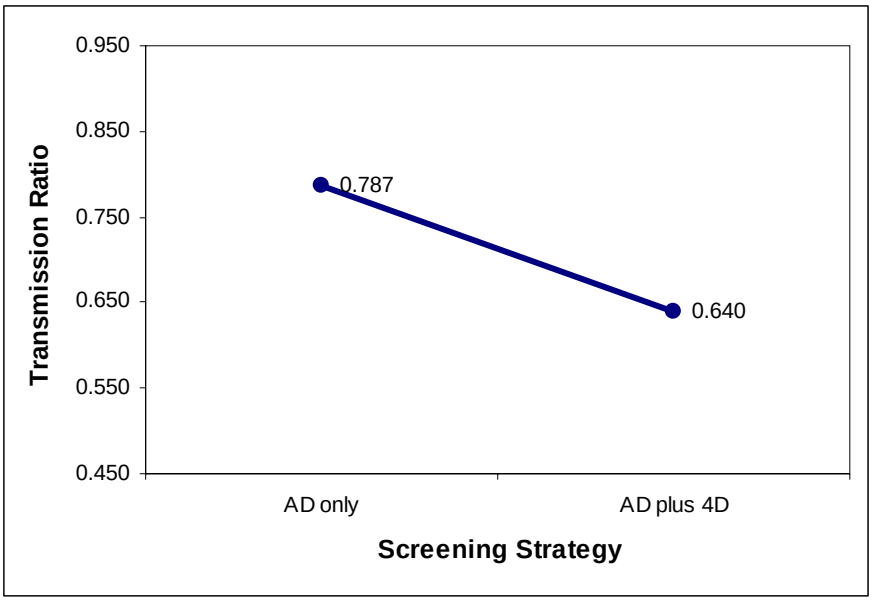

Figure 6.11 Main effect of the screening strategy

The practical implication of the significant negative main effect of the screening strategy is that the introduction of repeat screening test is a very effective policy to reduce MRSA transmission, given that the hospital has already introduced admission screening. However, more frequent screening tests may require enormous resources (e.g., additional laboratory capacity and technicians, increased work-load of nurses, logistics and communication challenges). Therefore, the additional costs associated with more frequent screening tests need to be considered.

Number of Isolation Beds

The number of isolation beds has a significant main effect and it is an effective intervention policy. On average, the transmission ratio is reduced by 0.093 (from 0.76 to 0.667) when the number of isolation beds in the ward is increased from zero to six (see Figure 6.12). The mean main effect is statistically significant (95% confidence level from -0.098 to -0.088) and a majority of individual estimates of the effect are negative (94.6% or 473 out of 500 individual estimates of the effect). Overall, the main effect is strong and consistent, and increasing the number of isolation beds is an effective intervention policy to reduce MRSA transmission.

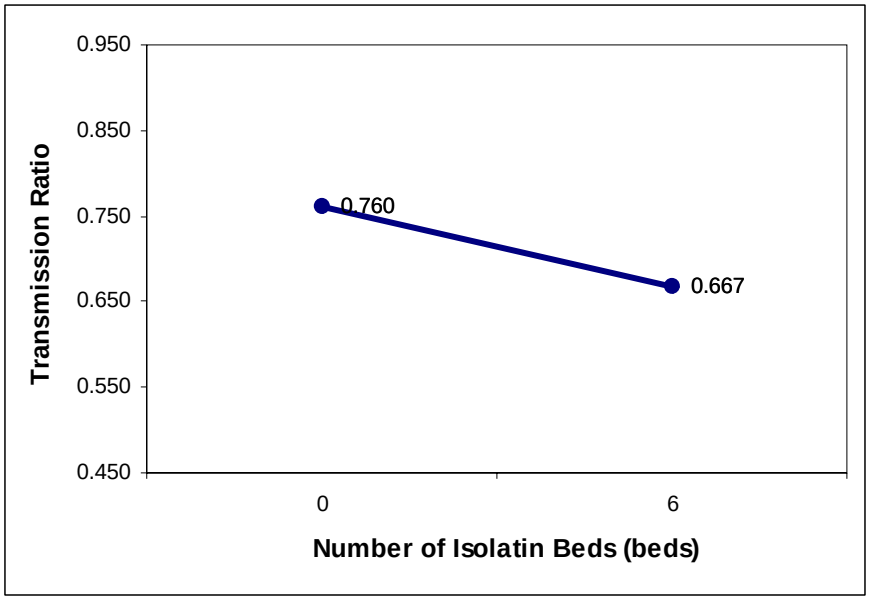

Figure 6.12 Main effect of the number of isolation beds

The practical implication of the significant main effect is that providing more isolation beds is an effective intervention policy for reducing MRSA transmission. However, the experimental results show that this policy is not as effective as the policies of adopting rapid screening test and introducing more frequent screening tests.

In reality and in the model, not all isolation beds are solely for the purpose of MRSA isolation and this may partially explain the relative ineffectiveness of this policy. In practice, extra financial costs of providing more isolation beds and the negative impacts on patients' welfare under isolation (e.g., reduced quality of care due to isolation and increased stress from isolation) need to be considered as well.

6.5.3 Analysis of Two-way Interaction Effects

The main effect can only reveal the average effect of each experimental factor on the model response. Two-way interaction effects, on the other hand, can reveal potential interactions between two experimental factors, i.e., how the level of one experimental factor will affect the effectiveness of the other experimental factor. If the two-way interaction effect is significantly different from zero, it indicates that the effectiveness of one factor is significantly dependant on the level of the other factor. Such information will provide valuable information to help hospital management make better informed decisions, especially when more than one intervention policy and influencing factor are considered at the same time.

Compared to main effects, two-way interaction effects have a smaller magnitude. Figures 6.2 and 6.3 show that two-way interaction effects are in general much closer to the zero horizontal line than main effects. Table 6.6 shows that while more than 90% of individual effects are either negative or positive for all eight main effects; more than 90% of individual effects are either negative or positive for only 7 out of 28 two-way interaction effects. It is not possible to discuss each of the 28 two-way interaction effects in detail, instead, only some significant or practically important effects are further investigated.

Transmission Coefficient and Length of Stay

The most significant two-way interaction is between the transmission coefficient and the average length of stay (see Figure 6.13). The mean interaction effect is statistically significant (95% confidence interval from 0.132 to 0.142), and nearly all individual estimates of the effect are positive (99.2%, or 496 out of 500 individual estimates of the effect). Figure 6.13 shows that when the average length of stay is at its base value of six days, the average transmission ratio is reduced by 0.559 (from 1.148 to 0.589) as the transmission coefficient changes from 0.15 to 0.10, considering all combination

of the other six experimental factors; while when the length of stay is at its alternative value of four days, the average transmission ratio is only reduced by 0.285 (from 0.701 to 0.416), considering all combination of other experimental factors. It is obvious that MRSA transmission is reduced more sharply by a lower transmission coefficient when the length of stay is longer. In another word, the effectiveness of transmission coefficient on reducing MRSA transmission depends on the level of the average length of stay. By definition, half of the difference between 0.559 and 0.285, or 0.137, is the two-way interaction effect between the two factors.

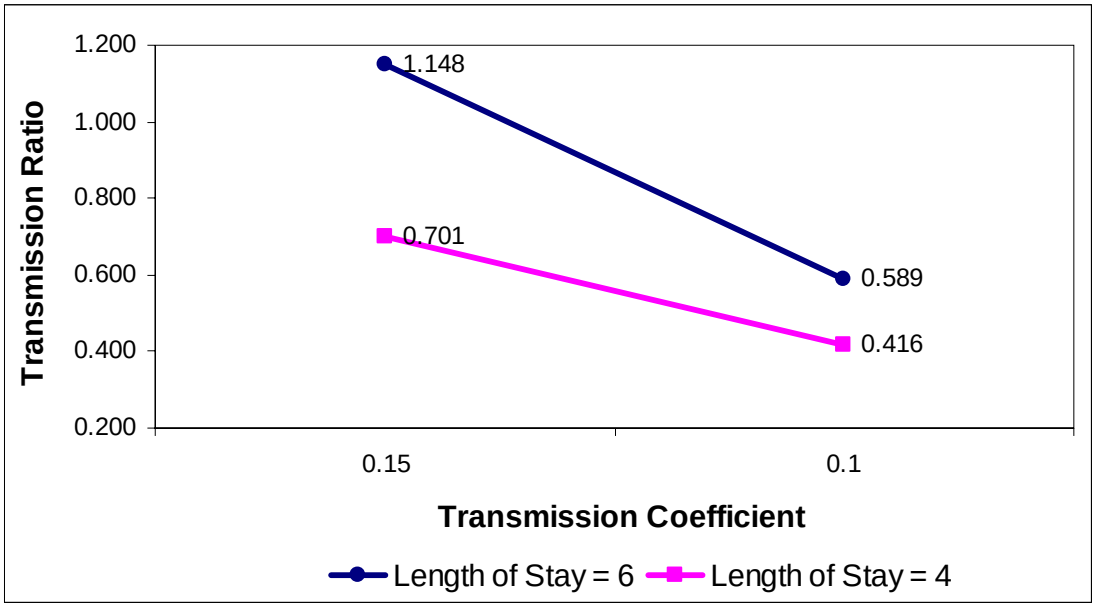

Figure 6.13 Two-way interaction effect between the transmission coefficient and the length of stay

It is difficult to control either the transmission coefficient or the patients' lengths of say. However, when it is possible to influence the two factors, the two-way interaction effect demonstrates how the two factors interact. The significant interaction effect between the two factors implies that, if possible, it is more effective to reduce the average length of stay where the transmission coefficient is high (e.g., in intensive care units or hospital wards where patients are more vulnerable to MRSA transmission). The effect also implies that, if possible, it is more effective to reduce the transmission coefficient where the patients' average length of stay is long.

Screening Strategy and Length of Stay

The second most significant two-way interaction is between the screening strategy and the average length of stay (see Figure 6.14). The mean interaction effect is statistically significant and a majority, or 95.2%, of all 500 individual estimates of the effect are positive. Figure 6.14 shows that when the average length of stay is six days, the average transmission ratio is reduced by 0.25 (from 0.994 to 0.581) as the screening strategy is changed from admission screening only to admission screening plus four day repeat screening, considering all combinations of other factors. When the average length of stay is four days, the average transmission ratio is only reduced slightly by 0.045 (from 0.581 to 0.536). Half of the difference between 0.25 and 0.045, or 0.103, is the two-way interaction effect between the two factors.

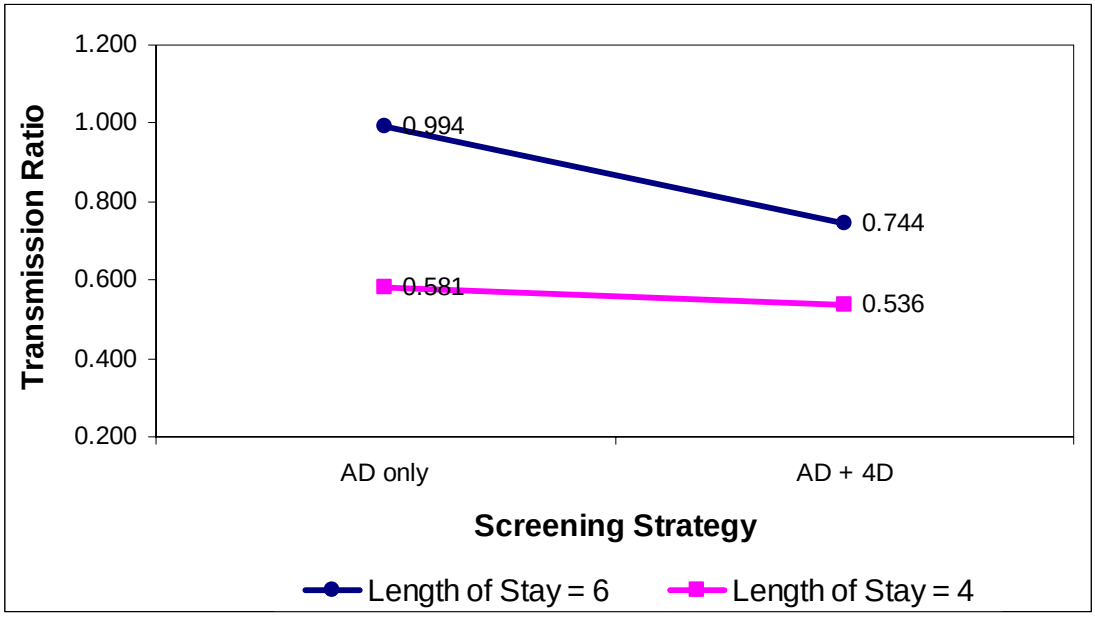

Figure 6.14 Two-way interaction effect between the screening strategy and the length of stay

The clear practical implication of the significant two-way interaction effect is that it is more effective to introduce repeat screening test in the hospital wards where the patients' average length of stay is long. For hospital wards where the patients' average length of stay is short, introducing repeat screening test may not significantly reduce MRSA transmission. Therefore, when resources are limited, repeat screening test should firstly be applied to those wards with longer patients' lengths of stay.

Test Turnaround Time and Transmission Coefficient

The next significant two-way interaction is between the test turnaround time and the transmission coefficient (see Figure 6.15). The mean effect is statistically significant and a majority, or 95.4%, of all 500 individual estimates of the effect are positive. Figure 6.15 shows that when the transmission coefficient is 0.15, the average transmission ratio is reduced by 0.385 (from 1.117 to 0.732) as the test turnaround time is reduced from four days to one day. When the transmission coefficient is 0.10, the average transmission ratio is reduced less sharply by 0.198 (from 0.601 to 0.404). Half of the difference between 0.385 and 0.198, or 0.094, is the two-way interaction effect between the two factors.

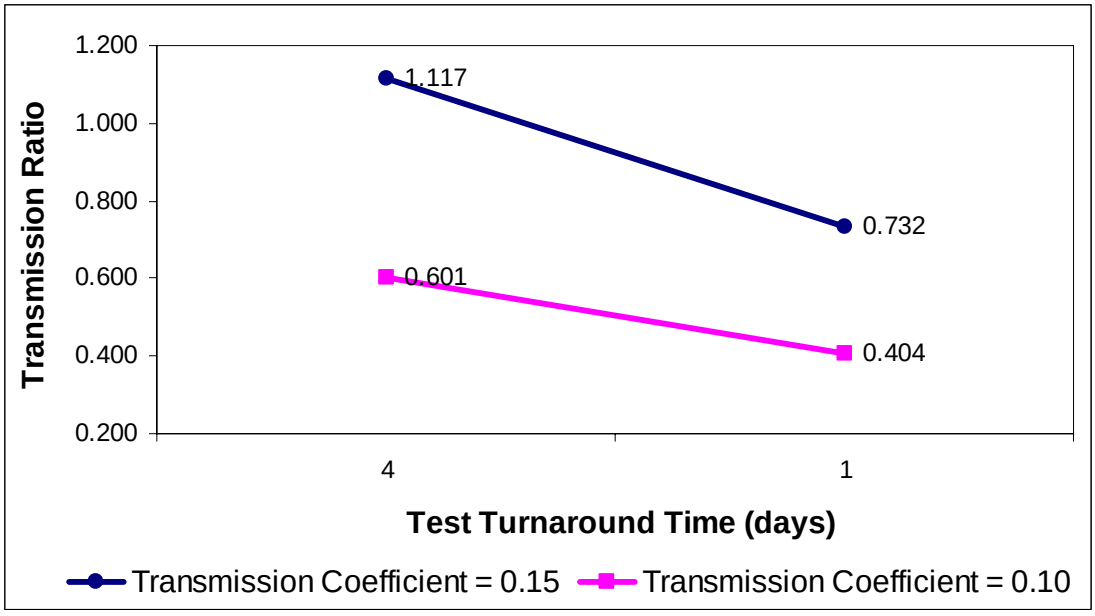

Figure 6.15Two-way interaction effect between the test turnaround time and the transmission coefficient

The practical implication of the interaction effect is that a rapid screening test (with a shorter test turnaround time) is more effective in the hospital units where the transmission coefficient is high. Therefore, when it is not possible to apply rapid screening test in the whole hospital, the limited resource should be allocated to places like intensive care units and hospital wards where patients are particular vulnerable to MRSA.

Transmission Coefficient and Endemic Setting

The next significant two-way interaction is between the transmission coefficient and the endemic setting (see Figure 6.16). The mean effect is statistically significant and a majority, or 94.4%, of all 500 individual estimates of the effect are negative. Figure 6.16 shows that when the endemic setting is 10%, the average transmission ratio is reduced by 0.337 (from 0.793 to 0.457) as the transmission coefficient is reduced from 0.15 to 0.10; while when the endemic setting is 2%, the average transmission ratio is reduced more sharply by 0.508 (from 1.056 to 0.548). Half of the difference between 0.337 and 0.508, or -0.086, is the two-way interaction effect between the two factors. Since the hospital only has limited control over the transmission coefficient and the endemic setting, the significant interaction effect between the two factors may have limited practical implications.

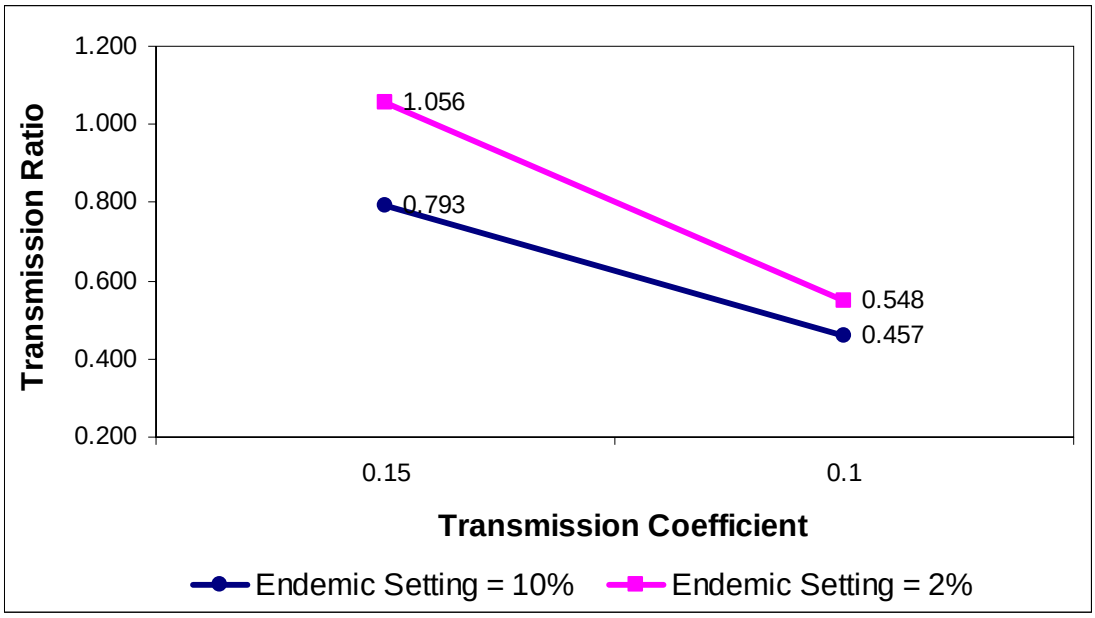

Figure 6.16 Main Two-way interaction effect between the transmission coefficient and the endemic setting

Test Turnaround Time and Length of Stay

The next significant and interesting two-way interaction is between the test turnaround time and the average length of stay (see Figure 6.17). The mean effect is statistically significant and a majority, or 93.2%, of all 500 individual estimates of the effect are positive. Figure 6.17 shows that when the average length of stay is six days, the average transmission ratio is reduced by 0.372 (from 1.055 to 0.683) as the test turnaround time is reduced from four days to one day. When the average length of

stay is four days, the average transmission ratio is reduced less sharply by 0.21 (from 0.663 to 0.453). Half of the difference between 0.372 and 0.21, or 0.081, is the two-way interaction effect between the two factors.

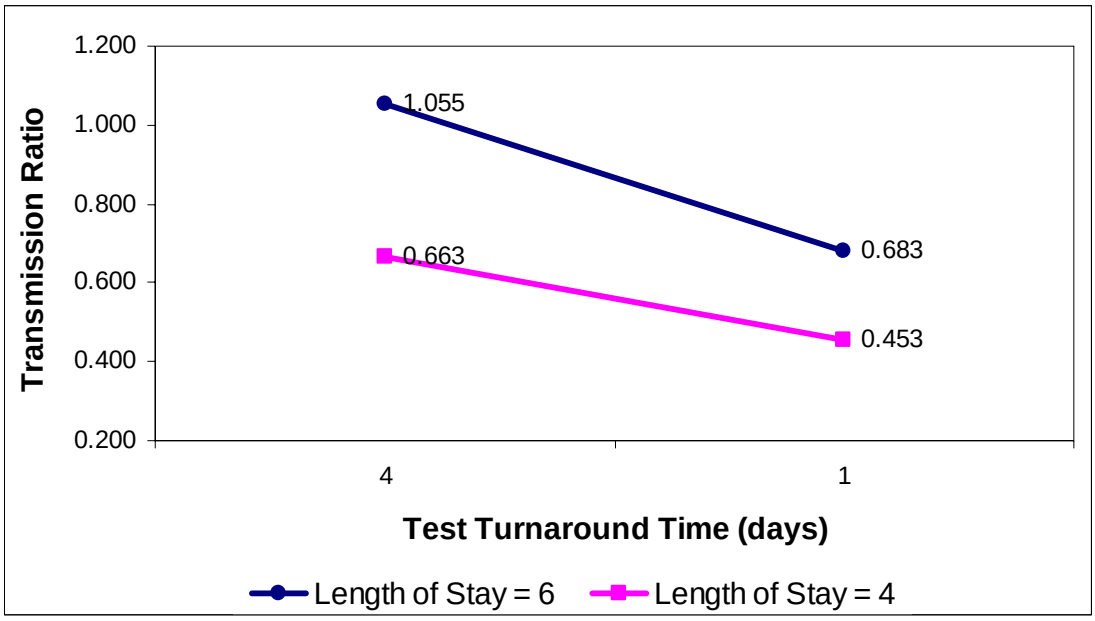

Figure 6.17 Two-way interaction effect between the test turnaround time and the length of stay

The practical implication of the interaction effect is that a rapid screening test is more effective in hospital units where the patients' average length of stay is long. Therefore, like the implementation of repeat screening tests, when it is not possible to adopt rapid screening tests in the whole hospital, the limited resource should be allocated to hospital units where the patients' average length of stay is long.

Screening Strategy and Transmission Coefficient

The next significant two-way interaction is between the screening strategy and the transmission coefficient (see Figure 6.18). The mean effect is statistically significant and a majority, or 92%, of all 500 individual estimates of the effect are positive. Figure 6.18 shows that when the transmission coefficient is 0.15, the average transmission ratio is reduced by 0.228 (from 1.039 to 0.811) as the screening strategy is changed from admission screening only to admission screening plus four day repeat screening. When the transmission coefficient is 0.10, the average transmission ratio is only reduced by 0.067 (from 0.536 to 0.469). Half of the difference between 0.228 and 0.067, or 0.08, is the two-way interaction effect between the two factors.

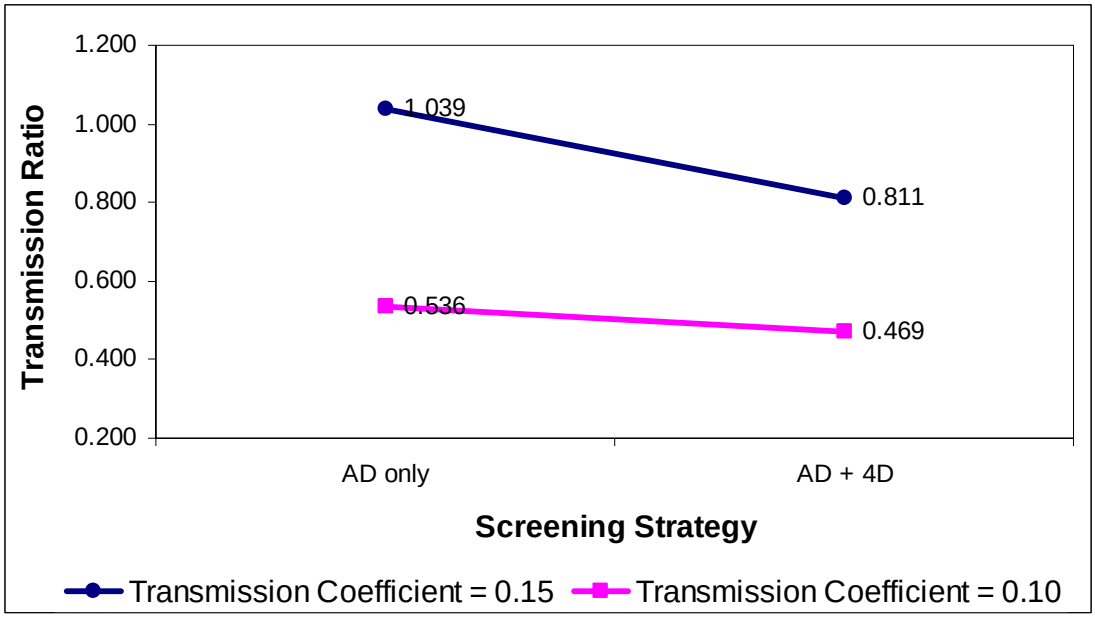

Figure 6.18 Two-way interaction effect between the screening strategy and the transmission coefficient

The practical implication of the interaction effect is that the introduction of repeat screening test is more effective in the hospital units where the transmission coefficient is high. Therefore, like the policy of adopting rapid screening test, when it is not possible to introduce repeat screening test in the whole hospital, the limited resource should be allocated to places like intensive care units and hospital wards where patients are particular vulnerable to MRSA.

Number of Isolation Beds and m

The mean two-way interaction effect between the number of isolation beds and the factor *m* (i.e., the proportion of transmission coming from within the same bay) is statistically significant and a majority, or 88.2%, of all 500 individual estimates of the effect are negative (see Figure 6.19). This interaction effect includes two experimental factors that have not been discussed so far in the analyses of two-way interaction effects. Figure 6.19 shows that when the factor of *m* is 0.1, the average transmission ratio is only slightly decreased by 0.025 (from 0.801 to 0.777) as the number of isolation beds increased from zero to six. When *m* is 0.9, the average transmission ratio is reduced significantly by 0.161 (from 0.719 to 0.557). Half of the difference between 0.025 and 0.161, or -0.068, is the two-way interaction effect between the two factors.

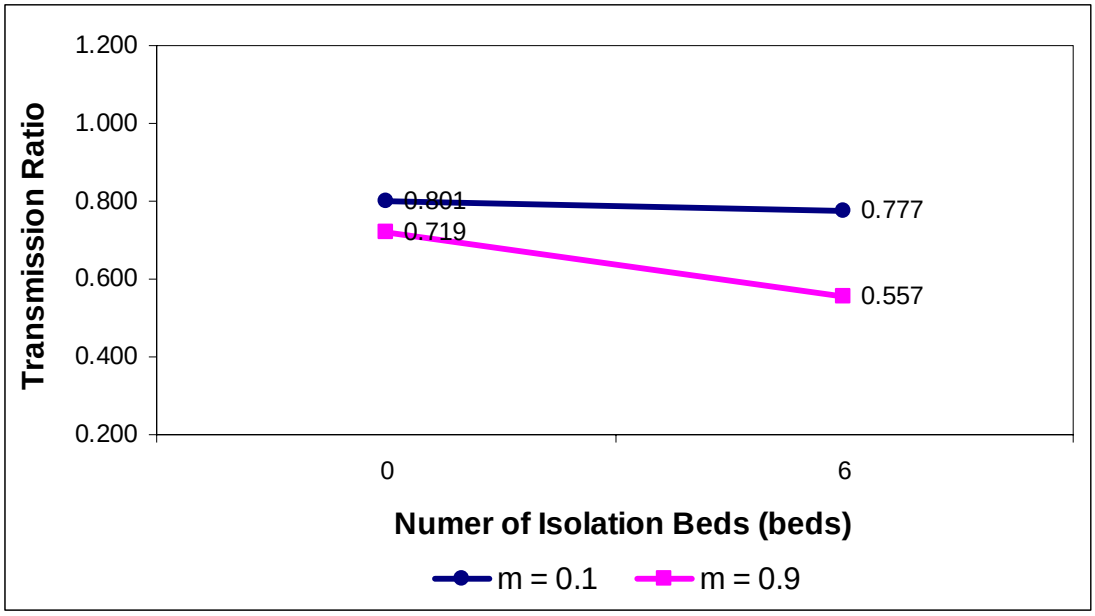

Figure 6.19 Two-way interaction effect between the number of isolation beds and the proportion of transmission within bay

The practical implication of the interaction effect is that adding extra isolation beds is only effective when the isolation room can be perfectly isolated from the rest of the ward (i.e., the value of factor *m* is high). When the isolation room can not be effectively isolated from the rest of the ward, adding extra isolation beds may be not effective in reducing MRSA transmission.

6.6 Model Experimentation: Response Surface Design

The limitation of the factorial design is that only two levels are tested for each experimental factor and therefore linearity is implicitly assumed. In order to study the experimental factors in more detail and capture the potential non-linear relationships between experimental factors and the model response and the non-linear interactions among different experimental factors, response surface design is applied.

It is practically not possible to carry out response surface design for each pair of experimental factors. Instead, three pairs of experimental factors, which all show significant two-way interaction effects and have potential practical implications, are selected. Other pairs of experimental factors can be studied using the same method. The selected pairs of experimental factors are:

- The screening strategy and the average length of stay;

- The test turnaround time and the average length of stay; and
- The number of isolation beds and the proportion of transmission within the ward bay.

The average length of stay and the number of isolation beds, which are included in the response surface design, may implicitly change the ward occupancy, especially when they take extreme values. In order to exclude the impact of different levels of ward occupancy on MRSA transmission, the ward occupancy is fixed at 90% in every design point of the response surface design. The constant ward occupancy level is achieved by adjusting the patient arrival rate according to Equation 6.1. Equation 6.2 shows how the patient arrival rate is calculated for each scenario in the response surface design.

$$\textit{(Patient Arrival Rate)} = \textit{(Number of Beds in Ward)} \times \textit{(Average Ward Occupancy)} / \textit{(Average Length of Stay)} \quad (6.2)$$

Screening Strategy and Length of Stay

There is a significant two-way interaction effect between the screening strategy and the mean length of stay. The interaction between the two factors also has practical implications since the screening strategy can be controlled by the hospital and the patients' lengths of stay can be easily measured. In the response surface design, five screening strategies will be tested: no screening at all, admission screening only, admission screening and weekly repeat screening, admission screening and four day repeat screening, and admission screening and daily repeat screening. The mean length of stay will be set at five levels: two, four, six, eight and ten days. Overall, the design matrix consists of 25 design points and the mean transmission ratio of each design point is estimated based on 500 replications (see Table 6.7). The response surface is shown in Figure 6.20.

Table 6.7 Response surface design matrix between the screening strategy and the length of stay

		Screening strategy				
		No screening	Admission screening only	Admission and weekly screening	Admission and four day screening	Admission and daily screening
The average length of stay (days)	2	0.505	0.373	0.37	0.369	0.361
	4	1.295	0.692	0.651	0.633	0.593
	6	2.5	1.147	0.939	0.85	0.768
	8	4.445	2.063	1.178	1.042	0.928
	10	7.249	3.624	1.429	1.186	1.024

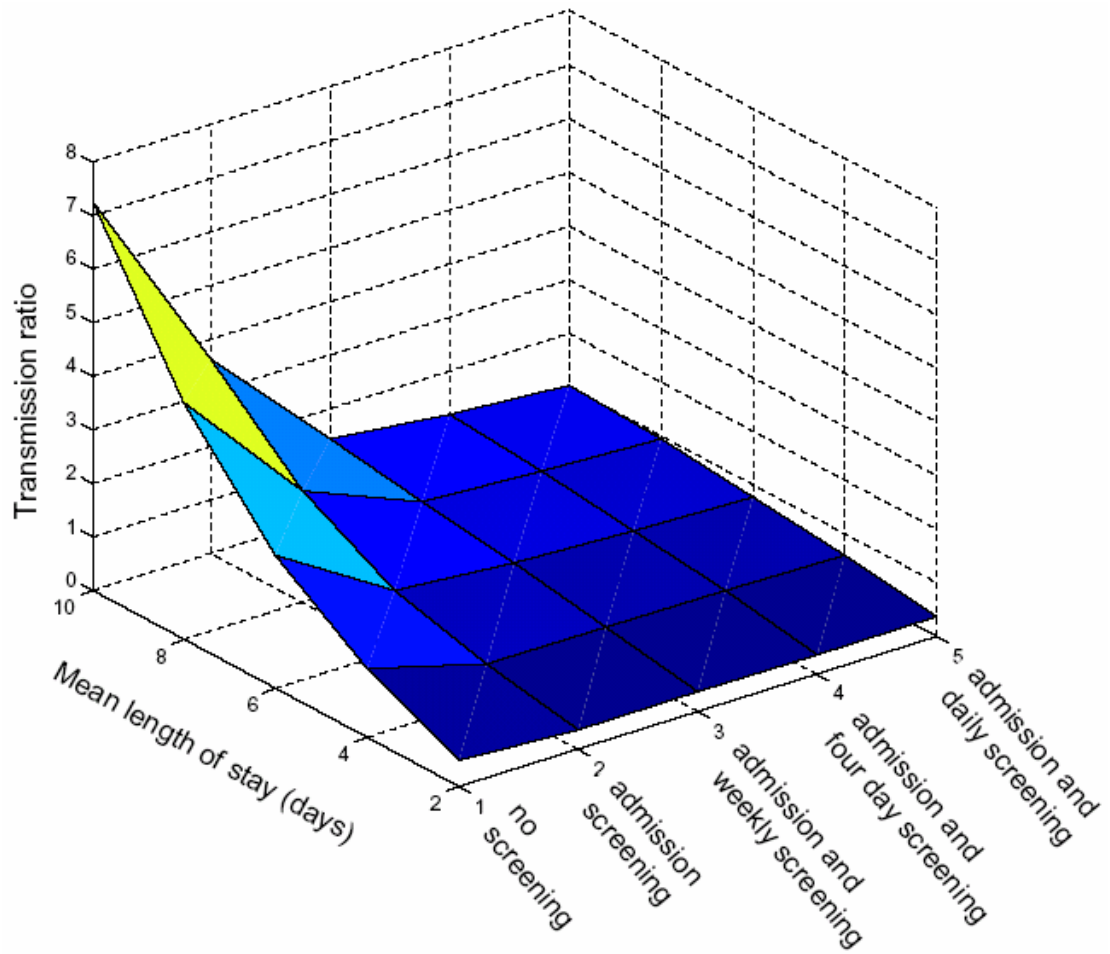

Figure 6.20 Response surface between the screening strategy and the length of stay

The response surface shows that overall transmission ratio is lower with more frequent screening test and shorter average length of stay. Strong interactions and non-linear relationships between the two factors and the transmission ratio are also uncovered. When the average length of stay is fixed, the transmission ratio drops

sharply when the screening strategy changes from no screening to just admission screening; the reduction of transmission ratio is significantly smaller when the screening strategy changes from admission screening and four day screening to admission screening and daily screening. For example, when the average length of stay is 6 days, the transmission ratio is reduced significantly by 1.353 (from 2.5 to 1.147) or 54.1% when the admission screening is introduced, while the transmission ratio is reduced only slightly by 0.082 (from 0.85 to 0.768) or 9.6% when four day repeat screening is replaced by daily repeat screening.

Furthermore, the non-linear relationship between the screening strategy and the transmission ratio is more apparent when the mean length of stay is longer (e.g., 6, 8 or 10 days) rather than shorter (e.g., 2 or 4 days). A practical explanation is that, while the change from no screening at all to just admission screening may make a big difference under any level of length of stay, making the screening test more frequent (e.g., from four day repeat screening to daily repeat screening) will only be effective if patients stay in the ward long enough. For example, when the average length of stay is 8 days, the transmission ratio is reduced significantly when no screening is replaced by admission screening (from 4.445 to 2.063) and when admission screening is replaced by admission and weekly repeat screening (from 2.063 to 1.178). However, when the average length of stay is 4 days, while the transmission ratio is still reduced significantly when no screening is replaced by admission screening (from 1.295 to 0.692), the ratio is not reduced significantly when weekly repeat screening is introduced (from 0.692 to 0.651). When the screening strategy changes from weekly to four day or from four day to daily repeat screening, the effect on the transmission ratio is relatively not significant regardless of the level of mean length of stay (see the last three columns of Table 6.7 and Figure 6.20). It is not possible to identify these findings from the previous factorial design where only two levels are tested for each factor.

The practical implication of the response surface analysis is that, if a hospital does not have any pre-emptive screening test for MRSA, it is very effective to reduce MRSA transmission by even just introducing admission screening. When admission screening is already in practice, the introduction of repeat screening will only significantly reduce MRSA transmission if the average length of stay is long relative

to the interval of the repeat screening. When repeat screening is already available, making the repeat screening more frequent may not significantly reduce MRSA transmission even when the average length of stay is long. The experimental results support the NHS's recent screening policy which makes admission screening (for elective patients) compulsory for NHS hospitals in the UK.

Test Turnaround Time and Length of Stay

There is a significant two-way interaction effect between the test turnaround time and the length of stay which also has meaningful practical implications since test turnaround time represents an important intervention policy. In the response surface design, the turnaround time of the test will be set at six different levels from zero to five days and the average length of stay will be set at five levels: two, four, six, eight and ten days. Overall, the design matrix consists of 30 design points (see Table 6.8) and the response surface is shown in Figure 6.21.

Table 6.8 Response surface design matrix between the test turnaround time and the length of stay

		Test turnaround time (days)					
		0	1	2	3	4	5
The average length of stay (days)	2	0.256	0.322	0.372	0.41	0.435	0.451
	4	0.41	0.525	0.637	0.721	0.8	0.876
	6	0.52	0.697	0.852	1.008	1.147	1.266
	8	0.614	0.822	1.038	1.24	1.527	1.673
	10	0.663	0.949	1.216	1.477	1.794	2.125

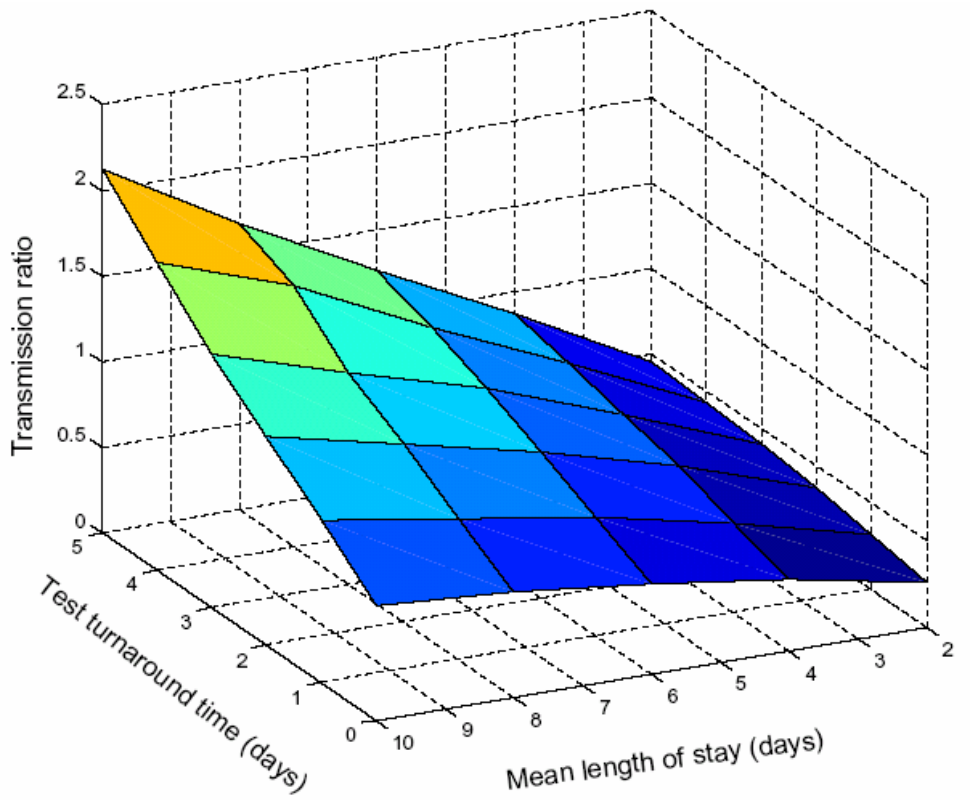

Figure 6.21 Response surface between the test turnaround time and the length of stay

The response surface shows that the overall transmission ratio is lower with faster screening test and shorter average length of stay. When the average length of stay is fixed, the transmission ratio is reduced rather linearly with the decrease of the test turnaround time; the speed of decrease, however, is faster when the average length of stay is longer. For example, when the average length of stay is eight days, the transmission ratio is reduced steadily by 1.059 (from 1.673 to 0.614) as the test turnaround time is shortened from five to zero days; when the average length of stay is two days, the transmission ration is reduced rather linearly only by 0.195 (from 0.451 to 0.256). This result complies with the two-way interaction effect of the two factors (see Figure 6.17).

When the test turnaround time is fixed, a non-linear relationship between the average length of stay and the transmission ratio can be spotted. The response surface shows that although the transmission ratio increases with longer average length of stay, the rate of the increase is diminishing or slowing. For example, when the test turnaround time is fixed at two days, the transmission ratio is increased by 0.265 (from 0.372 to 0.637) or 71.2% when the average length of stay increases from two to four days;

while the transmission ratio is only increased by 0.178 (from 1.038 to 1.216) or 17.1% when the average length of stay increases from eight to ten days. Such a diminishing increasing rate is also seen when the test turnaround time is set at other levels.

The practical implication of the response surface design is that MRSA transmission can be reduced significantly if the turnaround time of the screening test can be reduced under any level of length of stay, although the effectiveness is more significant with longer length of stay. The linear relationship between the test turnaround time and the transmission ratio means, regardless of the current test turnaround time, reducing the test turnaround time further (e.g., from four to three days or from two to one days) can always expect a significant reduction of MRSA transmission. This complies with and strengthens the finding from the main effect analysis that test turnaround time is the single most significant intervention policy (among the policies tested) to reduce MRSA transmission in the hospital setting.

Number of Isolation Beds and m

The last two experimental factors to be further explored by response surface design are the number of isolation beds and the proportion of the transmission coming from within the same bay, or *m*. The hospital can control the provision of isolation facilities and the two factors have natural connections since the factor of *m* is also the indicator of how isolated is the isolation room to the rest of the ward. In the response surface design, the number of isolation beds will be set at five different levels: zero, two, four, six and eight isolation beds. The factor of *m* will be set at six levels: 0, 0.2, 0.4, 0.6, 0.8 and 1. Overall, the design matrix consists of 30 design points (see Table 6.9) and the response surface is shown in Figure 6.22.

Table 6.9 Response surface design matrix between the number of isolation beds and the proportion of transmission within the bay

		The number of isolation beds (beds)				
		0	2	4	6	8
Proportion of transmission within bay and isolation room (*m*)	0	1.489	1.486	1.452	1.476	1.45
	0.2	1.465	1.419	1.402	1.367	1.343
	0.4	1.455	1.334	1.296	1.251	1.187
	0.6	1.411	1.289	1.214	1.134	1.076
	0.8	1.33	1.199	1.132	1.044	0.982
	1	1.24	1.125	1.038	0.95	0.895

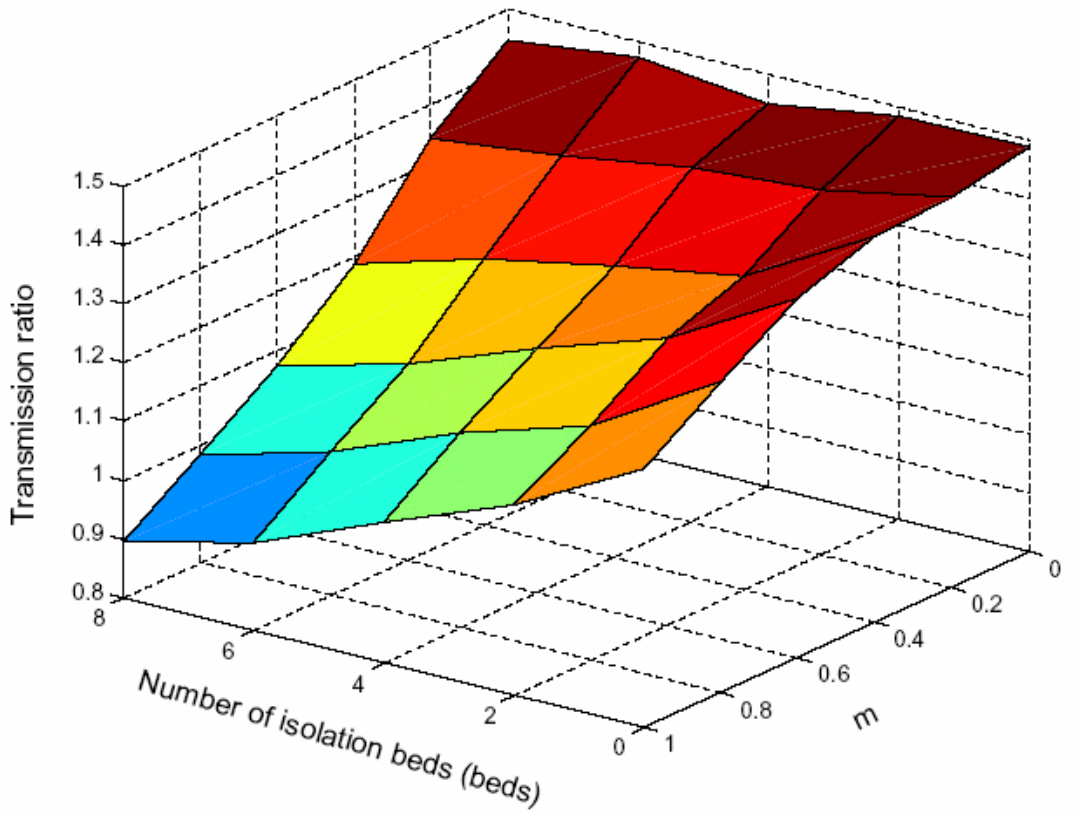

Figure 6.22 Response surface between the number of isolation beds and the proportion of transmission within the bay

The main and two-way interaction effects demonstrate that the transmission ratio is lower with more isolation beds and higher proportion of transmission coming within the same bay. The response surface shows in detail how the effectiveness of providing isolation beds is dependent on the level of *m*. When *m* is zero (i.e., all transmissions are caused by the ward level interactions and isolating patients can not prevent MRSA from spreading), the transmission ratio remains fairly stable (ranges from 1.45 to 1.489 with no clear upward or downward trends) when the number of isolation beds changes between zero and eight. When *m* is one (i.e., all transmission are caused by local contacts within the same bay and patients in isolation can neither acquire nor spread MRSA), the transmission ratio is reduced sharply from 1.24 to 0.895 as the number of isolation beds increases from zero to eight. When *m* takes values between zero and one, the transmission ratio is also reduced significantly as the number of isolation room increases, and the reduction in the transmission ratio is more evident with higher value of *m*. From another perspective, when there are no isolation beds in the ward, the transmission ratio decreases slightly from 1.489 to 1.24 as *m* increases from zero to one. However, as isolation beds are introduced, the transmission ratio is

reduced more sharply as *m* increases from zero to one. For example, when six isolation beds are added, the transmission ratio is reduced significantly from 1.476 to 0.95, as *m* increases from zero to one.

The non-linearity relationship between the number of isolation beds and the transmission ratio is also demonstrated by the response surface. For example, when *m* is set at 0.6, 0.8 and 1, as the number of isolation beds increases from zero to eight, the transmission ratio will firstly drop quickly as the first two isolation beds are added, then the transmission ratio decreases slowly when additional isolation beds are provided (see Table 6.9 and Figure 6.22). For example, when *m* is 0.6, the introduction of the first two isolation beds reduces the transmission ratio by 0.122 (from 1.411 to 1.289), the introduction of the next two isolation beds (i.e., from two to four isolation beds) reduces the ratio by 0.075 (from 1.289 to 1.214), and the transmission ratio is only reduced slightly by 0.058 (from 1.134 to 1.076) when the number of isolation beds increases from six to eight.

The practical implication of the response surface design is that the more effective isolation can prevent MRSA transmission from spreading (i.e., the value of *m* is closer to one), the more effective of the intervention policy of adding more isolation beds. Another practical implication is that it is more effective to provide the first few isolation beds than providing additional isolation beds when some isolation beds are already available in the ward. Therefore, when the total number of isolation facilities that can be provided is fixed (probably due to a constrained budget), it is more effective to make sure that every hospital unit has a few isolation beds (i.e., isolation facilities are distributed among the hospital) rather than a few hospital units have an excessive number of isolation facilities.

6.7 Summary

6.7.1 Indications to the Management of MRSA

According to the results from the model experimentation, the following conclusions and indications are generalised regarding the effective management of MRSA in the

hospital setting. The indications focus on the intervention polices that the hospital management may actually control.

Rapid Screening Test

The factor of the test turnaround time has the most significant main effect among the three intervention polices tested. In general, MRSA transmission can be significantly reduced by the introduction of rapid screening test in the hospital setting.

The effectiveness of rapid screening tests is dependent on the level of other factors including the transmission coefficient and the average length of stay. When it is not possible to apply rapid screening tests in the whole hospital, the limited resource should be allocated to places like ICUs and hospital wards where patients are particularly vulnerable to MRSA and where the patients' average length of stay is long. Furthermore, the response surface design shows that, regardless of the current level of the length of stay, reducing the test turnaround time further can always result in a significant reduction of MRSA transmission.

Pre-emptive Screening Test

Screening strategy has the second most significant main effect among the factors representing intervention policies. Like the policy of the rapid screening test, the effectiveness of the screening strategy is also dependent on the average length of stay and the transmission coefficient. A number of screening strategies (including no pre-emptive screening at all) are tested by the response surface design. The analysis shows that the choice of the most effective screening strategy is highly dependent on the current practice of screening strategy and the patients' average length of stay.

Providing Isolation Facilities

The factor of the number of isolation beds also has a significant main effect, although it is not as effective as the factors of the test turnaround time and the screening strategy. The effectiveness of proving more isolation beds is significantly dependent on the proportion of transmission coming within the same ward bay, or m. Experimental results show that adding extra isolation beds is only effective when the isolation room can be perfectly isolated from the rest of the ward (i.e., the value of m is high). The response surface design demonstrates that it is more effective to provide

the first few isolation beds than providing additional isolation beds when some isolation beds are already in place.

6.7.2 Limitations of Methods

The main experimental design method used for the research is fractional factorial design. The method only tests two levels of each experimental factor and assumes linear relationships between the experimental factor and the model response.

As only two levels of each factor are tested and the effectiveness of the experimental factor is determined by changing the value from the base to the alternative level, the choice of the levels will significantly affect the experimental results. If the two levels selected are too close, the effectiveness of the factor may be underestimated. The effectiveness may also be overestimated if the two levels chosen are too further apart. In this study, the base and alternative levels of each experimental factor are carefully selected so that the difference between the two levels of each factor is significant while not unrealistic and unachievable in practice. In order to ensure the comparability of the effectiveness across all experimental factors, the same relative differences between the two levels of each factor is maintained. Despite the efforts to choose the most appropriate levels for experimental factors, the experimental results from the factorial design will have limitations and need to be interpreted by always referencing the selected base and alterative levels of each factor.

The linearity assumption of the factorial design may also affect the interpretation of the experimental results. It is possible that the impact of the experimental factor on the model response is non-linear, as demonstrated by the response surface design (e.g. between screening strategy and transmission ratio). Under such circumstances, the factorial design may only provide a rough picture of the relationship between the factor and the model response, while hiding the true non-linear relationship which may have important practical implications. For example, the factorial design shows that replacing admission screening with four day repeat screening will significantly reduce MRSA transmission; while the detailed response surface design shows that much of the reduction may be achieved by only replacing with weekly repeat screening. In practice, the weekly repeat screening may be less costly than the four day repeat screening. Due to the linearity assumption, results from the factorial design

may need to be further refined by an experimental design method that allows for non-linear relationships to be disclosed (e.g. response surface design).

Chapter 7

Model Extensions

7.1 Introduction

In this chapter, the MRSA model proposed in the previous chapters will be extended to study the transmission dynamics when two competing infectious diseases are explicitly modelled simultaneously, when multiple hospital units and HCWs are represented, and when the wider community is included. The main purpose of this model extension is to explore the possibility and ability of ABS to study MRSA and potentially other types of HAIs in a wider context.

In the first attempt to extend the model, apart from MRSA, the infectious disease of *Clostridium difficile* (*C. difficile*) is also explicitly modelled. Therefore, a patient may have either MRSA or *C. difficile* or both of them during the hospital ward stay. The two infectious diseases may compete for scarce infection control resources such as isolation facilities. In the second model extension, the original single ward model is extended to include three hospital units and HCWs are explicitly represented as agents. Therefore, the transmission dynamics among different hospital units and the role of HCWs can be studied. In the last model extension, not only the hospital ward but also the wider community, where the patients are admitted from and discharged to, is represented. The interactions between the hospital and its community are modelled and, as a result, the wider and longer term transmission dynamics of MRSA can be investigated.

7.2 Competitive Infections

In reality, more than one type of infectious disease may be present in the hospital environment. When infection control resources are limited (e.g., isolation facilities), patients who are colonised with one type of infectious disease may compete for these

scarce resources with patients who are colonised with other types of infections. For example, a patient who requires isolation due to MRSA colonisation may not be isolated if the isolation facility is occupied by a patient who is colonised with *C. difficile*. Such competition may affect the transmission dynamics of both infectious diseases.

No previous modelling studies have represented two types of HAIs in a single model. The model extension in this section attempts to explicitly model two competing infections (MRSA and *C. difficile*) in a single model and test how the competition between the two infections for isolation facilities may affect the transmission dynamics of both infections. Without clinical evidence, the extension model assumes that the transmissions of two infections are independent.

7.2.1 *Clostridium difficile*

C. difficile is a spore-forming Gram-positive anaerobic bacillus that was first isolated from stools of neonates in 1935 (Barbut and Petit 2001). Among healthy people, the asymptomatic carriage rate is about 3%; and the carriage rates are higher in patients with previous hospitalisation (10-25%) or in patients who have previously received antibiotics (10-20%) (Bartlett 1994). The clinical presence of *C. difficile* may range from mild diarrhoea to life-threatening pseudomembranous colitis and possible perforation. Currently, *C. difficile* is the leading cause of nosocomial infectious diarrhoea in adults and it is responsible for large outbreaks (Cartmill *et al*. 1994). *C. difficile* infection may increase the length of stay of an adult patient by 8 days (Spencer 1998) and an extra cost of about £4,107 (Wilcox *et al.* 1996).

More than 90% of *C. difficile* infections occur after or during antibiotic treatment. Antibiotics act by disrupting the normal colonic flora, allowing *C. difficile* to establish itself in the colon and proliferate. The antibiotics most likely to incur *C. difficile* are the broad-spectrum antibiotics that have a large impact on the normal intestinal flora which include penicillin, cephalosporin and clindamycin. A combination of antibiotics and long duration of the course increases the risk of developing *C. difficile* (Barbut and Petit 2001). Other risk factors of *C. difficile* include age, ICU admission, chemotherapy and length of stay.

Patients with symptomatic or asymptomatic *C. difficile* can both contaminate their immediate hospital environment and the spores may persist for several months on surfaces. Contamination is found to be significantly higher in hospital units with symptomatic patients than with asymptomatic patients (McFarland *et al.* 1990). Transmission of *C. difficile* can occur by direct contact with contaminated surfaces and via the hands of HCWs. In general, transmission of *C. difficile* from patient to patient is easy and spores play a key role since they can survive several months in the environment.

Dedicated intervention polices to prevent and control *C. difficile* may include the restrictive use of antibiotics (especially those that are considered at high risk for *C. difficile* infection), pre-emptive screening tests, isolation and treatment of infected patients. General measures to prevent and control HAIs should also be implemented to reduce the transmission of *C. difficile* in the hospital setting (see Section 1.2.3). Treatment of asymptomatic patients was not recommended by some studies (Johnson *et al.* 1992).

7.2.2 Model Modifications

Previous modelling studies have focused on MRSA or *C. difficile*. There has been no study that attempts to represent the two infectious diseases simultaneously in the same model. In the first model extension, the original model which focuses only on MRSA will be extended to include a second infectious disease, i.e., *C. difficile*. The two infectious diseases will compete for scarce hospital resources and may potentially interact with each other in other ways (e.g., the presence of MRSA may increase the risk of acquiring *C. difficile* and vice versa).

The main modifications to the original MRSA model are to add additional states and state transitions of *C. difficile* since, a patient agent will have two separate and parallel state transitions in the extended model, one regarding MRSA colonisation status and the other regarding *C. difficile* colonisation status. Another modification to the original model is that isolation beds in the modified model will be solely designated to patients who are identified as colonised with either MRSA or *C. difficile*. Compared to the original MRSA model, the parameter which represents the possibility that isolation beds may be used with a purpose other than controlling MRSA is discarded.

By doing this, the utilisation of the isolation beds can be more realistically represented and monitored. Other additional assumptions of the extended model include:

- On admission, a patient is either colonised with *C. difficile* or not;
- Screening tests of *C. difficile* are carried out only on admission and there are no repeat screening tests (which means secondary cases of *C. difficile* can not be detected);
- Patients who are detected as colonised with *C. difficile* by admission screening tests will be isolated if isolation beds are available;
- There is no decolonisation treatment for *C. difficile* following detection;
- Once MRSA is successfully cleared by decolonisation treatment, the patient, if he/she stays in an isolation bed, will not be transferred back to a ward bay if colonisation of *C. difficile* has been detected; and
- Detected *C. difficile* positive patients have reduced transmissibility compared to undetected patients colonised with *C. difficile*.

Regarding the states and state transmissions of *C. difficile*, the colonisation status of a patient is either colonised or susceptible and the detection states include undetected and detected. A primary case patient of *C. difficile* (i.e., colonised with *C. difficile* on admission) will change the detection state from undetected to detected if an admission screening test is performed and when the positive result is reported. Following detection, the patient may be isolated if an isolation bed is available, and if so, the patient will remain in isolation until discharge. A *C. difficile* susceptible patient may acquire the infection during the ward stay and any resulting secondary case will remain undetected during the rest of the ward stay (since there are no repeat screening tests). The main states and state transitions of a patient regarding both MRSA (which are the same as Figure 4.2) and *C. difficile* (the right-hand side of the diagram) are illustrated in Figure 7.1.

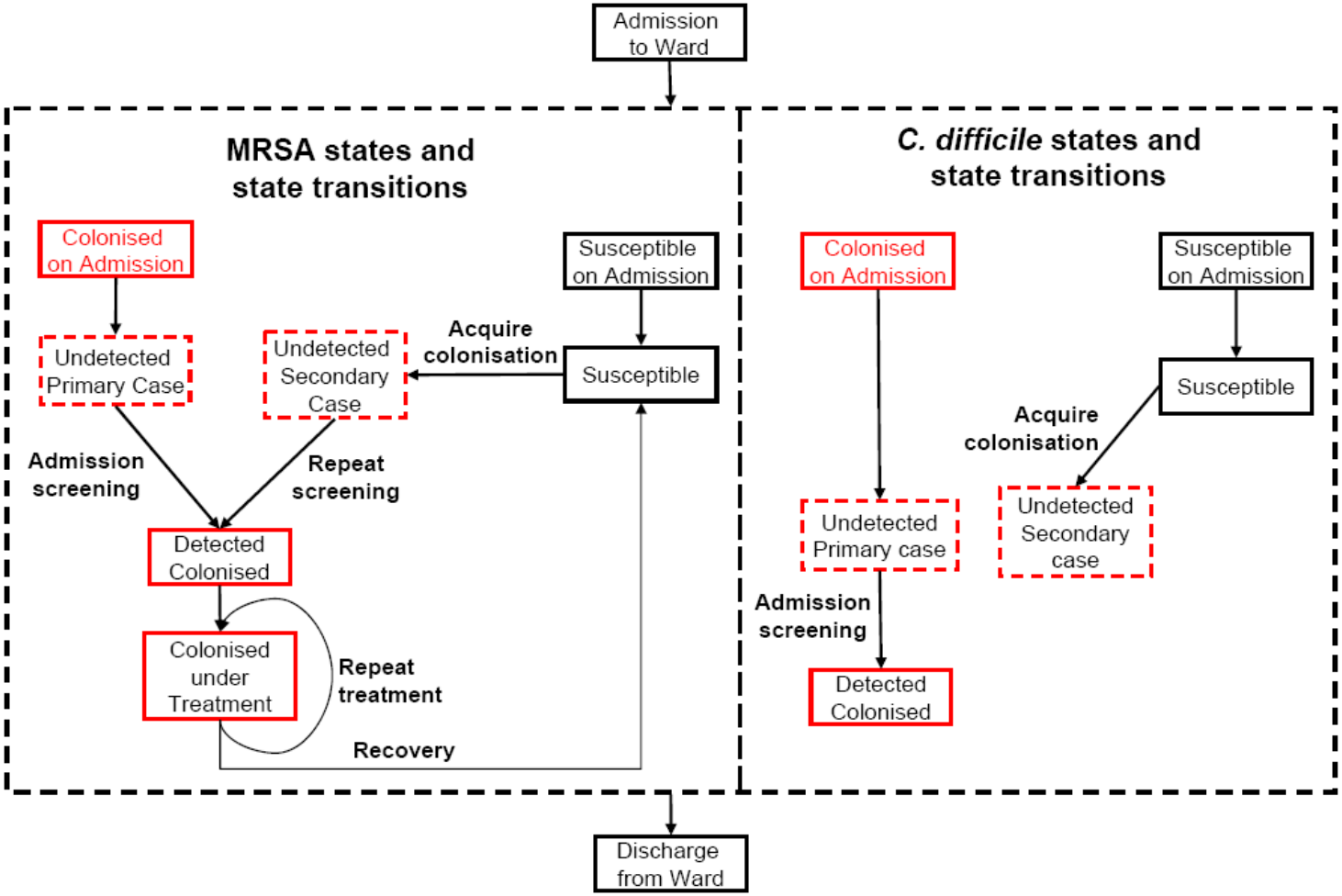

Figure 7.1 Patient main states and state transitions of MRSA and C. difficile

Additional input parameters, their default values and the sources of the default values are shown in Table 7.1. Most of the input parameter values are based on previous studies. The proportion of patients who have already been colonised with *C. difficile* on admission and the transmission coefficient of *C. difficile,* or C_1, are assumed to be 10% and 0.2 respectively (Barbut and Petit 2001). The turnaround time of the screening tests of *C. difficile* is assumed to be 3 days (Samore *et al.* 1994). The effectiveness of *C. difficile* detection, or k_1, is set at 0.4 which assumes that detection may reduce 60% of the infectivity of a colonised patient. The reduced infectivity may be due to enhanced barrier precautions.

Table 7.1 Additional model input parameters for model extension of competitive infections

Parameter	Default value	Symbol	Source
Proportion of *C. difficile* colonisation on admission	10%		Barbut and Petit 2001
Test turnaround time of *C. difficile* screening test (days)	3		Samore *et al.* 1994
Transmission coefficient of *C. difficile*	0.2	C_1	Barbut and Petit 2001
Effectiveness of *C. difficile* detection on reducing infectivity	0.4	k_1	Assumption

The way to calculate the transmission probabilities of *C. difficile* is the same as MRSA in the original model (see Section 4.5.1 and Table 4.1) where the pairwise action assumption, modified based on the mass action assumption, is applied. In each time slice, pairs of susceptible and colonised *C. difficile* patients are formed and evaluated separately and independently, and the transmission probability of the susceptible patient in the pair is estimated. Apart from the transmission coefficient of *C. difficile*, or C_1, the transmission probability is affected by the detection state of the colonised patient in the pair (detected patient has reduced infectivity represented by the parameter of k_1) and the relative location of the two patients (within the same ward bay or not). The modified equations for calculating the rate of *C. difficile* colonisation of the susceptible patient are given in Table 7.2. The transmission probability can then be calculated based on Equation 3.3. Due to the lack of clinical evidence, the extended model assumes that the transmissions of MRSA and *C. difficile* are independent.

Table 7.2 Equations for calculating the rate of C. difficile colonisation of the susceptible patient

Scenarios	Colonised patient	Susceptible patient	Transmission probability
1	Undetected	Same bay	$\lambda_1(\Delta t) = C_1 \cdot \left(\frac{m}{n_{bay} - 1} + \frac{1-m}{n_{ward} - 1} \right) \cdot \Delta t$
2	Undetected	Other bays/Isolation	$\lambda_1(\Delta t) = C_1 \cdot \frac{1-m}{n_{ward} - 1} \cdot \Delta t$
3	Detected	Same bay	$\lambda_1(\Delta t) = C_1 \cdot k_1 \cdot \left(\frac{m}{n_{bay} - 1} + \frac{1-m}{n_{ward} - 1} \right) \cdot \Delta t$
4	Detected	Other bays/Isolation	$\lambda_1(\Delta t) = C_1 \cdot k_1 \cdot \frac{1-m}{n_{ward} - 1} \cdot \Delta t$

7.2.3 Model Experimentation

Comparison between the Original and the Extended Model

As a type of scarce and expensive hospital resource, isolation beds are required by both MRSA and *C. difficile* patients in the extended model. Therefore, when the total demand for isolation beds exceeds the supply at any time, the two infectious diseases may compete with each other. In order to demonstrate the competition for the isolation beds and how the competition affect the utilisation of isolation beds and the transmission ratios of both infectious diseases, comparisons are made between the original model where isolation beds are solely for isolating MRSA patients and the extended model where isolation beds can be used for either MRSA or *C. difficile* patients. Please note the parameter of the availability of isolation beds in original model is discarded to make it comparable with the extended model which also does not include the parameter (see Section 7.2.2).

By changing the number of isolation facilities from zero to ten, Table 7.3 shows the average number of patients isolated due to MRSA in the original model. For the extended model, the table reports the average number of patients isolated due to MRSA and *C. difficile*, and the average total number of patients been isolated. Each mean value is estimated from 500 replications with each replication lasts for 415 days (50 days warm-up and 365 days for data collection).

Table 7.3 Average number of patients isolated in the original and the extended models

Number of isolation beds	Original model	Extended model		
	Isolated (MRSA)	Isolated (MRSA)	Isolated (*C. difficile*)	Isolated (total)
0	0.0	0.0	0.0	0.0
1	29.5	19.9	26.5	46.4
2	48.8	37.5	47.2	84.7
3	58.1	49.8	61.7	111.5
4	62.5	57.4	70.5	127.9
5	64.1	60.7	74.4	135.1
6	65.5	63.3	76.3	139.6
7	65.6	63.4	78.0	141.4
8	65.2	64.4	78.2	142.6
9	65.0	63.6	77.4	141.0
10	65.1	64.0	78.0	141.9

Figure 7.2 illustrates the comparison diagrammatically by showing the number of patients isolated due to MRSA in the original and the modified model, and the total number of patients isolated in both models with different numbers of isolation beds. For the original model, the number of patients isolated due to MRSA and the total number of patients isolated are represented by the same line (the black line). For the modified model, the difference between the number of patients isolated due to MRSA (the dotted line at the bottom) and the total number of patients isolated (the dotted line on the top) represents the number of patients isolated due to *C. difficile*.

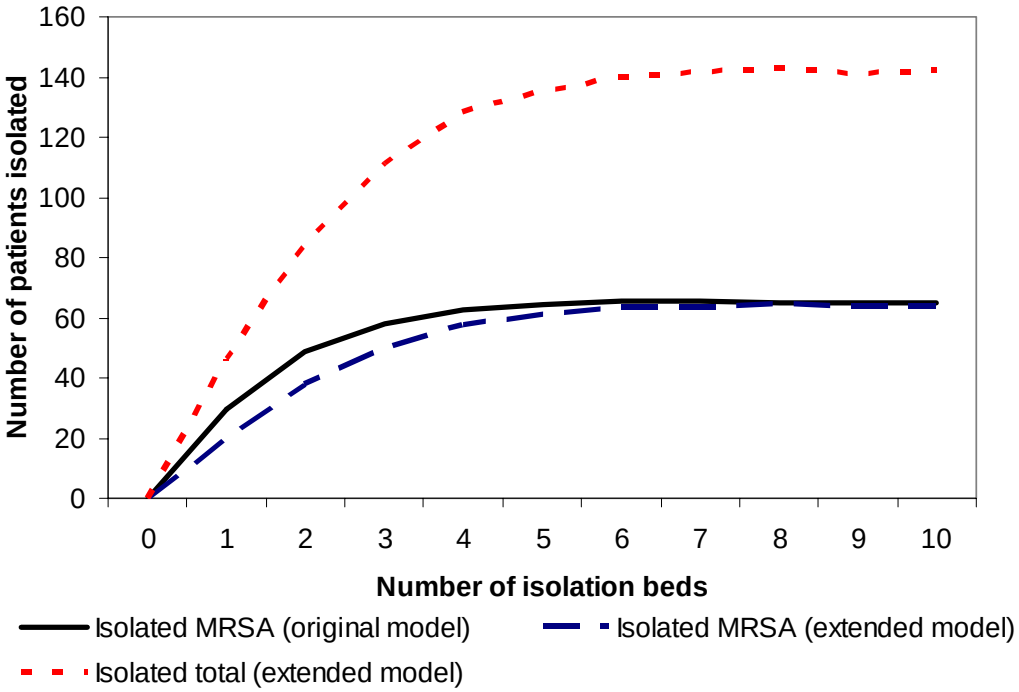

Figure 7.2 Comparison of the number of patients isolated between the original and the extended model

The results demonstrate that, given the same number of isolation beds (except zero which means no isolation at all), the average total number of patients isolated is significantly higher in the extended model than the original model (compare the dotted line on the top and the black line in Figure 7.2). The reason is that the isolation facilities are more fully utilised by serving the patients colonised with both MRSA and *C. difficile* rather just for MRSA patients.

Apart from demonstrating the impact of including a competitive infection on the utilisation of isolation beds, the impact on the transmission ratio of MRSA is also investigated. By changing the number of isolation facilities from zero to ten, Table 7.4 and Figure 7.3 show the average transmission ratios of MRSA in the original and the extended model.

Table 7.4 Average transmission ratios of MRSA in the original and the extended models

Number of isolation beds	Transmission ratio of MRSA (original model)	Transmission ratio of MRSA (extended model)
0	1.022	1.017
1	0.879	0.930
2	0.808	0.870
3	0.734	0.789
4	0.711	0.741
5	0.695	0.700
6	0.687	0.695
7	0.695	0.694
8	0.679	0.691
9	0.686	0.690
10	0.693	0.684

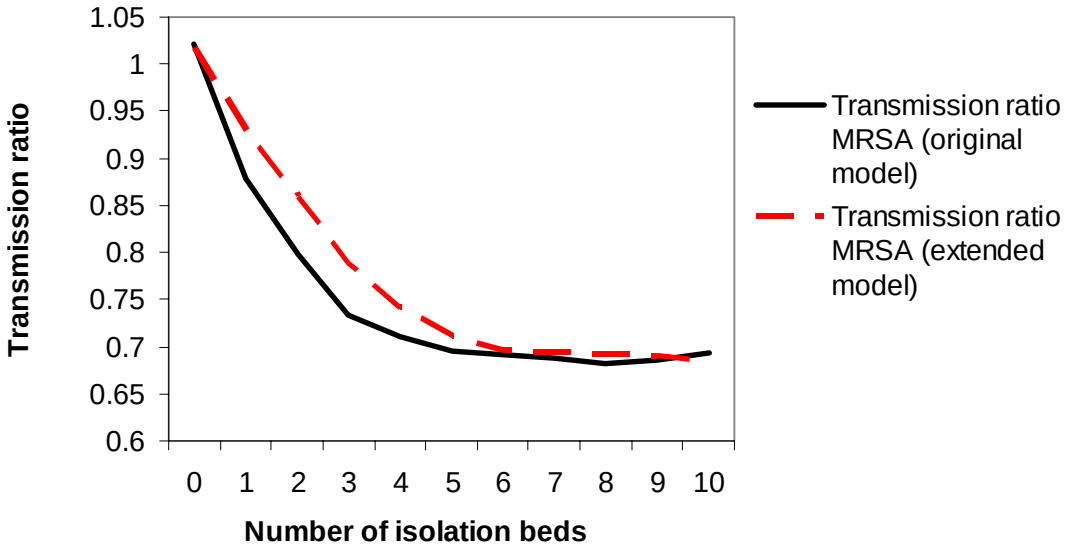

Figure 7.3 Comparison of the transmission ratios of MRSA between the original and the extended model

The results demonstrate that, when only a few isolation beds are available, the average transmission ratio of MRSA is significantly higher in the extended model than the original model. As the number of isolation beds increases further, the difference of the transmission ratios between the original and extended model becomes smaller. This difference is demonstrated in Figure 7.3 by the initial bigger gap between the two lines with few isolation beds and then the merging of the two lines as the number of isolation beds increases further. The reason that the transmission ratio of MRSA is higher in the extended model with limited isolation beds is that fewer detected MRSA

patients are isolated due to the competition with *C. difficile* (see Figure 7.2). As the isolation facility increases, most detected MRSA patients will be isolated and the two lines begin to merge.

Full Factorial Design

Using the extended model of competitive infections, a simple full factorial design is used to study the impact of three key input parameters on the transmission dynamics of MRSA and *C. difficile*. The experimental factors are the transmission coefficient of MRSA (TCM), the transmission coefficient of *C. difficile* (TCC) and the number of isolation beds (ISO). The two model responses are the transmission ratio of MRSA and the transmission ratio of *C. difficile*. The base and alternative values of each experimental factor is given in Table 7.5 and the design matrix which contains eight design points (i.e., $2^3 = 8$) is shown in Table 7.6.

Table 7.5 Experimental factors and their base/alterative values for the model extension of competitive infections

Experimental factor	Index	Base value (-)	Alternative value (+)
Transmission coefficient of MRSA	1	0.15	0.1
Transmission coefficient of *C. difficile*	2	0.25	0.15
Number of Isolation beds (beds)	3	1	5

Table 7.6 Full factorial design matrix and model experimentation results for the model extension of competitive infections

Design point	Factor 1	2	3	Mean transmission ratio (MRSA)	Mean transmission ratio (*C. difficile*)
	TCM	TCC	ISO		
1	-	-	-	1.023	1.277
2	+	-	-	0.580	1.267
3	-	+	-	1.028	0.549
4	+	+	-	0.581	0.553
5	-	-	+	0.775	1.125
6	+	-	+	0.433	1.136
7	-	+	+	0.775	0.463
8	+	+	+	0.441	0.475

For each of the eight design points in the full factorial design, the model is run 500 replications with each lasting 415 days (50 days for warm-up and 365 days for data collection). The mean transmission ratios of MRSA and *C. difficile* are reported in Table 7.6. The average main and two-way interaction effects of the three experimental

factors on MRSA and *C. difficile* transmission ratios are estimated and given in Table 7.7 and 7.8. Apart from the mean, the dispersion and variation of the individual effects based on 500 replications are shown in Figure 7.4 and 7.5 in terms of first and third quartiles and the range.

Table 7.7 Average main and two-way interaction effects on MRSA transmission ratio for the model extension of competitive infections

	Factor 1	2	3
	TCM	TCC	ISO
Factor 1	X		
Factor 2	0.001	X	
Factor 3	0.054	0.000	X
Main effect	**-0.392**	**0.004**	**-0.197**

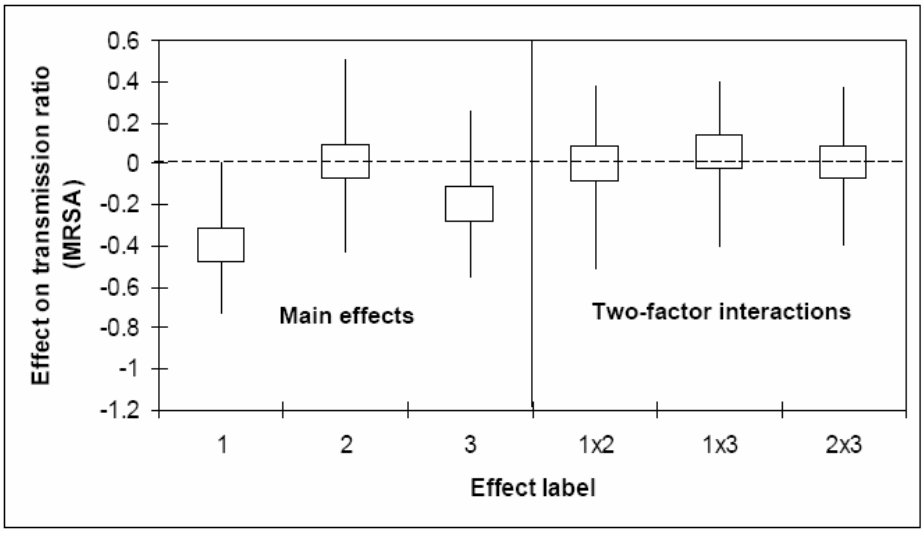

Figure 7.4 Quartiles and range of main and two-way interaction effects on MRSA transmission ratio for the model extension of competitive infections

Table 7.8 Average main and two-way interaction effects on C. difficile transmission ratio for the model extension of competitive infections

	Factor 1	2	3
	TCM	TCC	ISO
Factor 1	X		
Factor 2	0.004	X	
Factor 3	0.007	0.030	X
Main effect	**0.004**	**-0.691**	**-0.112**

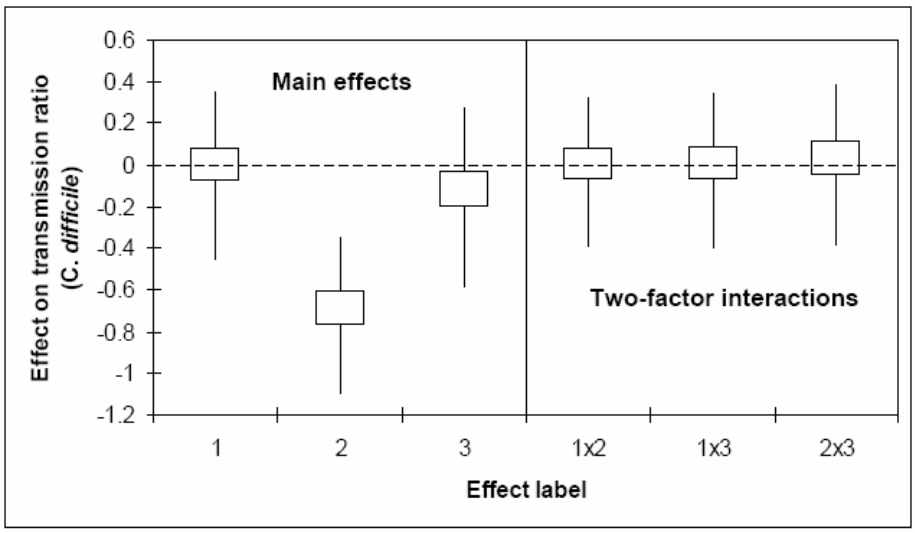

Figure 7.5 Quartiles and range of main and two-way interaction effects on C. difficile transmission ratio for the model extension of competitive infections

As expected, the transmission coefficient of MRSA has the most significant main effect on the transmission ratio of MRSA itself (i.e., the main effect is -0.392 which means the transmission ratio of MRSA can be reduced by 0.392 when the transmission coefficient of MRSA is reduced from 0.15 to 0.1) and the transmission coefficient of *C. difficile* has the most significant main effect on the transmission ratio of *C. difficile* itself (i.e., the main effect is -0.691 which means the transmission ratio of *C. difficile* can be reduced by 0.691 when the transmission coefficient of *C. difficile* is reduced from 0.25 to 0.15). The results of the main effects also demonstrate that the change of the transmission coefficient of MRSA has no significant impact on the transmission ratio of *C. difficile* (i.e., the main effect is 0.004) and the change of transmission coefficient of *C. difficile* also has no significant impact on the transmission ratio of MRSA (i.e., 0.004). This complies with the assumption of the extended model that the transmissions of two infections are independent. Finally, as expected, the number of isolation beds has a significant impact on both the transmission ratios of MRSA and *C. difficile* (i.e., the main effects are -0.197 and -0.112 respectively which means the transmission ratio of MRSA can be reduced by 0.197 and the transmission ratio of *C. difficile* by 0.112 when the number of isolation beds increases from one to five). The main effects of each of the three experimental factors on the two model responses (i.e., transmission ratios of MRSA and *C. difficile*) are shown in Figure 7.6, 7.7 and 7.8.

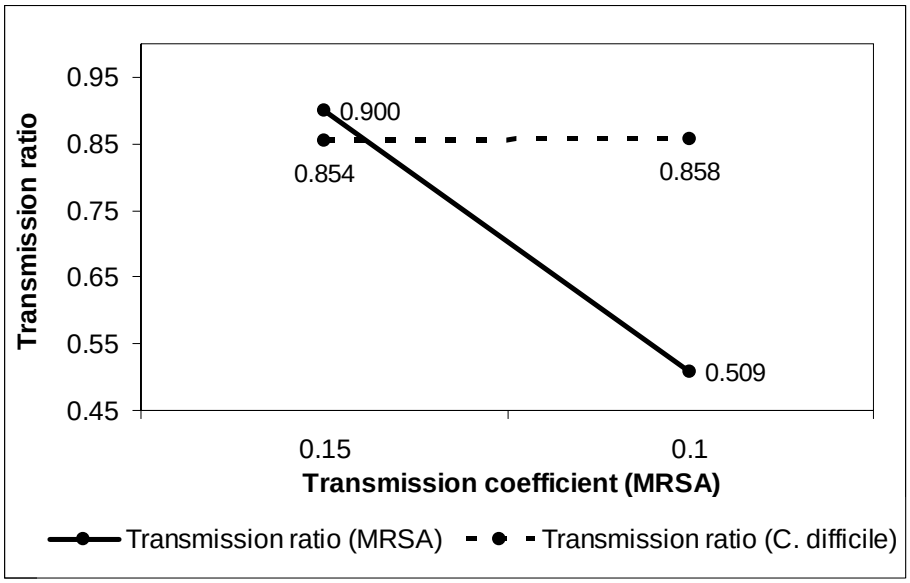

Figure 7.6 Main effects of MRSA transmission coefficient on transmission ratios of MRSA and C. difficile

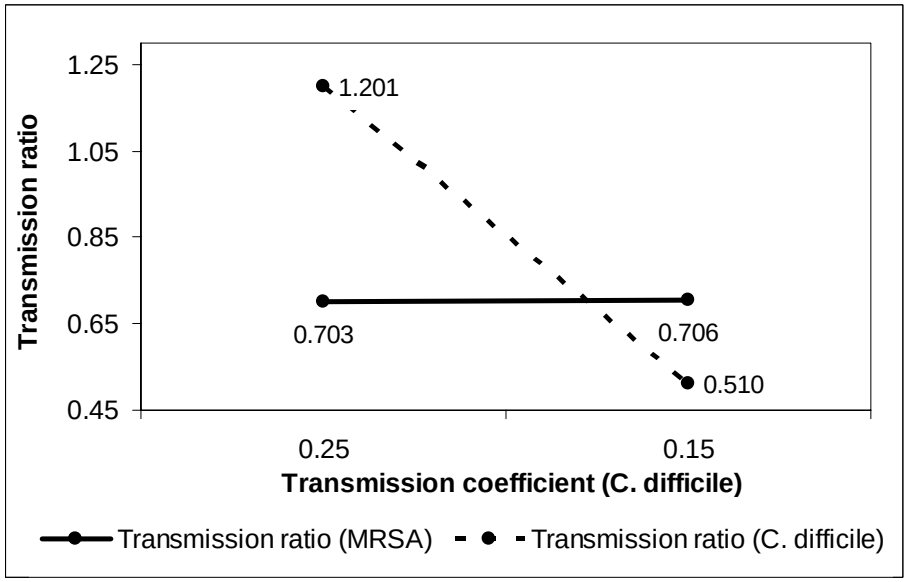

Figure 7.7 Main effects of C. difficile transmission coefficient on transmission ratios of MRSA and C. difficile

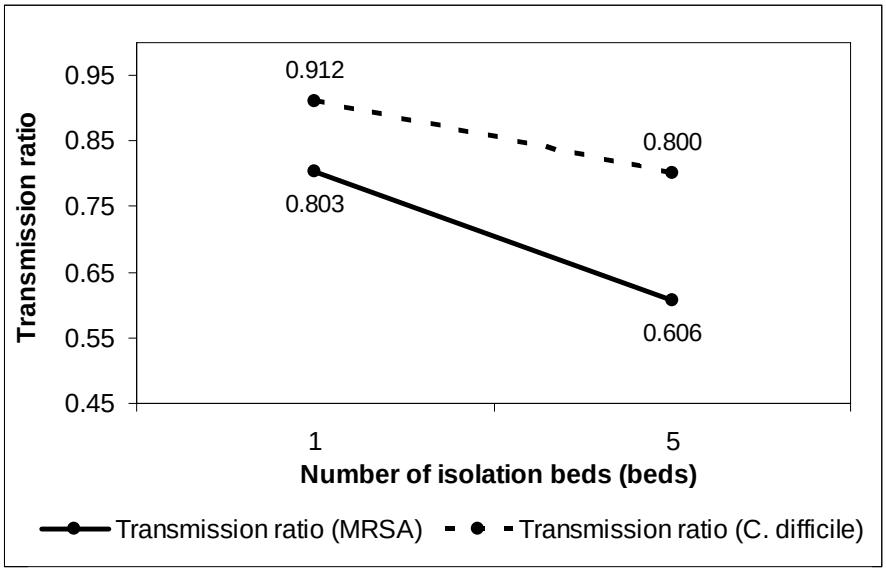

Figure 7.8 Main effects of the number of isolation beds on transmission ratios of MRSA and C. difficile

7.2.4 Conclusions

The model extension discussed in this section is the first attempt to model more than one infectious disease simultaneously in one model. By including a competitive infection, the competition between the two infections on scarce isolation resources and its impact on isolation utilisation and transmission dynamics can be studied.

The comparison results between the original and extended model show that the inclusion of a second infectious disease will significantly influence the utilisation of isolation facilities, both regarding the overall utilisation and the breakdown utilisation for each type of infection. The degree of the impact also depends on whether the isolation facilities are limited or abundant relative to the demand. Generally speaking, the scarcer the isolation resource is, the bigger the impact on the utilisation of the isolation beds and on the transmission dynamics of both infections. The conclusion should apply to other infection prevention and control resources such as nurses and special equipments.

7.3 Transmission Dynamics with Multiple Hospital Units and Healthcare Workers

The original MRSA model represents a single hospital unit and only patients are explicitly represented as agents. Since the MRSA empirical study is carried out on the ward basis and data are not available to describe or infer transmissions among different hospital wards, the original model does not include multiple hospital units and the potential interactions among them. Only the patient's MRSA colonisation status is monitored during the MRSA study and no data are collected about HCW's colonisation status, their contact patterns with patients, and their hand-washing frequency and efficacy. Therefore, it is not possible to model HCWs explicitly in the original model. To explore these modelling options, an extended model which includes three hospital units and explicitly represents HCWs is developed based on the original model. The extended model is mainly configured with hypothetical data. The main purpose of the model extension, however, is to demonstrate the ability and flexibility of ABS to model HAIs in these contexts.

7.3.1 Model Modifications

In reality, HAIs may not only be transmitted within a single hospital unit, but also between different hospital wards of the same hospital. The transmission among hospital units are normally facilitated by transiently colonised HCWs who may care for patients from different hospital units.

In the extended model, it is assumed that the scaled-down hospital has three hospital units. The ward layout of the three units is assumed to be the same as the hypothetical test ward defined in Chapter 6. It is also assumed that there are two types of HCWs. The activity of the first type of HCW is confined to a single hospital unit (e.g., nurses dedicated to a ward) and the activity of the second type of HCW involves all three hospital units (e.g., doctors who may contact patients in all hospital units). To focus on the role of HCWs in the transmission of MRSA, it is assumed that the only transmission route of MRSA is by cross transmission via transiently colonised HCWs. Therefore, both types of HCWs may transmit MRSA within the same hospital unit, while the second type of HCW may also transmit MRSA between different hospital units. Other assumptions of the extended model include:

- HCWs can only acquire MRSA colonisation through contact with colonised patients (i.e., there is no transmission among HCWs);
- Patients can only acquire MRSA colonisation through contact with colonised HCWs (i.e., patient can not acquire MRSA colonisation directly from other colonised patients);
- HCWs may only be transiently colonised and, once colonised, will be decolonised with a fixed rate through hand-washing;
- The numbers of both types of HCWs are fixed;
- Each patient each day needs a fixed number of contacts from HCWs, and the intervals between two successive contacts follow an exponential distribution;
- A proportion of the patient-HCW contacts is with Type 2 HCWs;
- Isolation can totally prevent transmission between HCWs and patients who are isolated;
- Patients who are receiving decolonisation treatment are less likely to transmit MRSA to HCWs;
- Patient may not move between different hospital units (they may still move within the ward).

Figure 9 illustrates the transmission dynamics of MRSA in a hospital with three hospital units. The figure shows that Type 1 HCWs interact locally with patients in the same ward; while Type 2 HCWs interact globally with every patient in the hospital. For each type of HCW, there are two states: colonised and susceptible. HCWs may acquire colonisation from contacts with colonised patients and may clear MRSA through hand-washing. For patient agents, most states and state transitions are the same as the original MRSA case study model (see Figure 4.2). The main difference is that patient in the extended model may only acquire MRSA colonised through contacts with colonised HCWs. The main states and state transitions of MRSA of the three types of agents (i.e., patient agents, Type 1 HCWs and Type 2 HCWs) are illustrated in Figure 7.10.

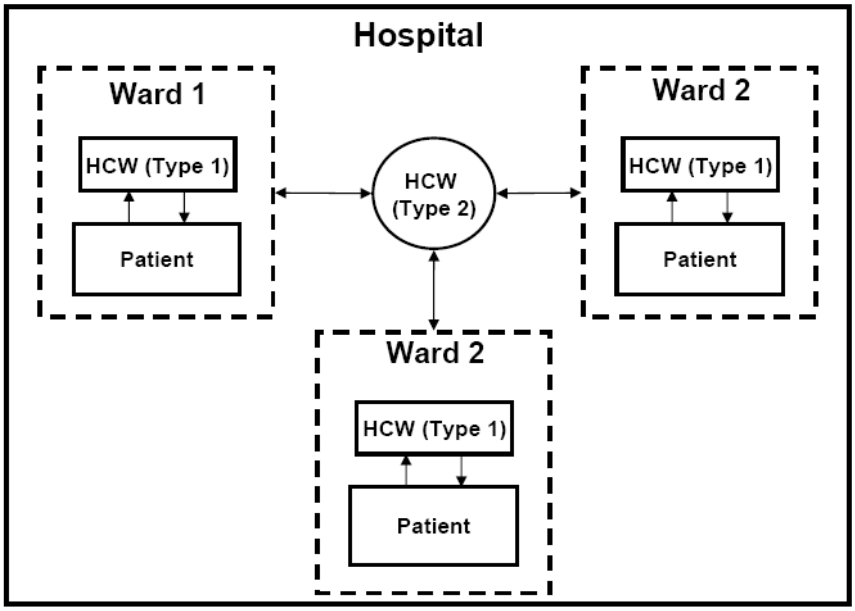

Figure 7.9 Transmission dynamics of MRSA in multiple hospital units

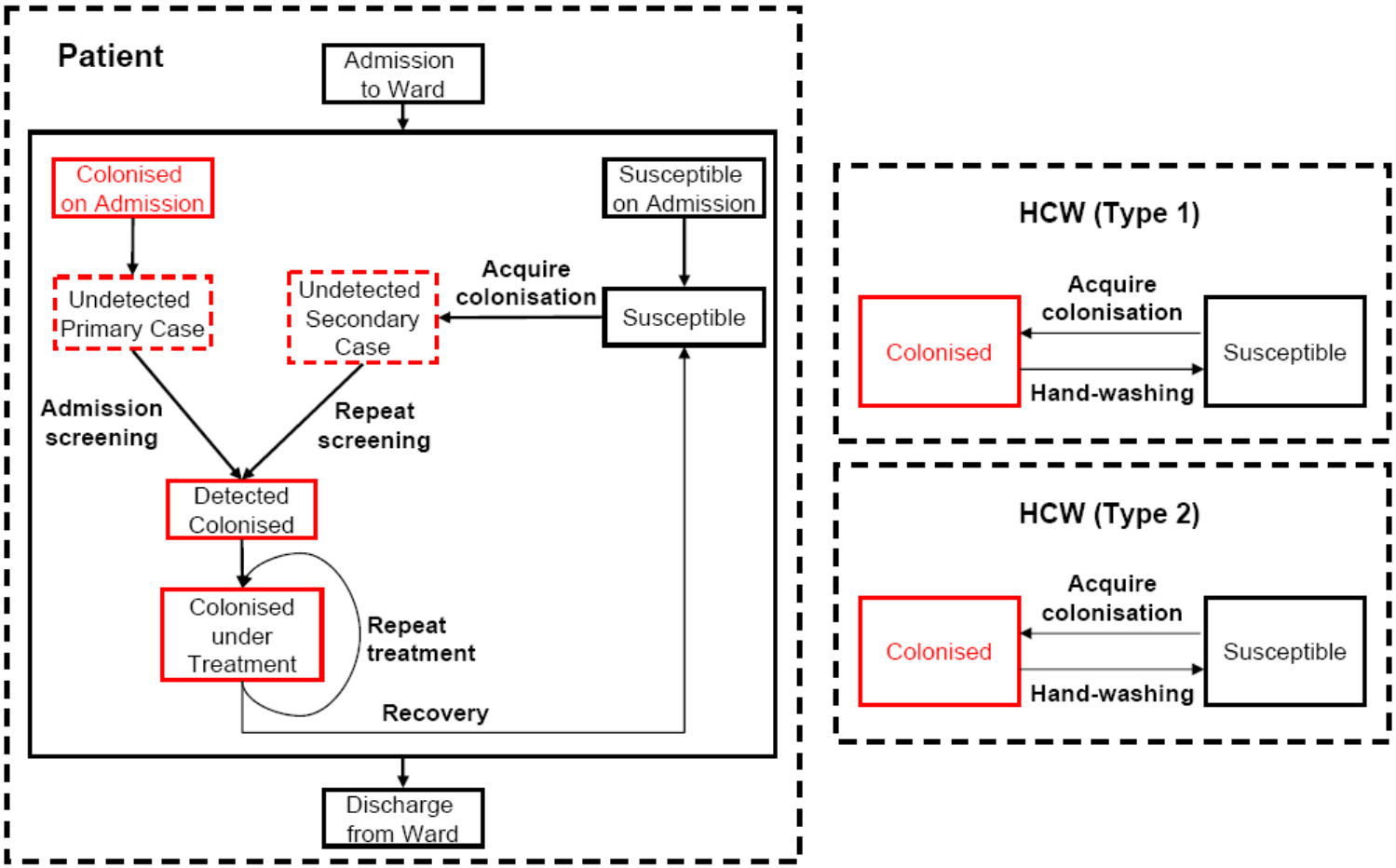

Figure 7.10 Main states and state transitions of MRSA of patients and HCWs in multiple hospital units

The new input parameters and their default values are given in Table 7.9. It is assumed that there are five Type 1 HCWs in each ward and five Type 2 HCWs in the whole hospital. On average, each patient in the ward requires five contacts per day with HCWs, among which 20% is assumed to be with Type 2 HCWs. The transmission probability of both patient-HCW and HCW-patient contacts is 0.1 which means there is a 10% chance that each contact may result in a successful transmission of MRSA, given that either the HCW or the patient is colonised with MRSA at the time of evaluation. For colonised HCWs, the hand-washing rate or the decolonisation rate is 14 times per day (Coope *et al.* 1999).

7.9 Additional model input parameters for model extension with multiple hospital units and healthcare workers

Parameter	Value	Source
Number of HCWs (Type 1)	5	Assumption
Number of HCWs (Type 2)	5	Assumption
Patient-HCW contact rate	5 / day	Cooper *et al.* 1999
Proportion of contacts with Type 2 HCWs	20%	Assumption
Patient-HCW contact transmission probability	0.1	Cooper *et al.* 1999
HCW-patient contact transmission probability	0.1	Cooper *et al.* 1999
Hand-washing rate (decolonisation rate)	14 / day	Cooper *et al.* 1999

The extended model adopts the host-vector model (see Section 3.7.1) to represent MRSA transmission. For each patient who stays in the ward, the time delay for the next contact with a HCW is sampled from an exponential distribution with the mean delay determined by the average contact rate specified in Table 7.9. When the scheduled contact is due, the model determines whether the contact is with Type 1 HCWs or Type 2 HCWs. Then, the patient will contact with a random HCW of the selected type. During evaluation, if the patient is colonised with MRSA but not in isolation and the HCW is not colonised with MRSA, then the HCW has a 10% chance of acquiring MRSA (the chance is reduced if the patient is under decolonisation treatment). If the HCW is colonised with MRSA and the patient is not colonised with MRSA and not in isolation, then the patient has a 10% chance of acquiring MRSA. For other situations (e.g., both the patient and the HCW are colonised with MRSA or both are not colonised with MRSA), the colonisation statuses of both the patient and the HCW will not change.

7.3.2 Model Experimentation

The extended model can be applied to study some intervention policies and experimental factors that are not possible in the original model. The three experimental factors that are to be tested include the number of Type 1 HCWs (or the HCW-patient ratio), the hand-washing rate (or the HCW decolonisation rate) and the transmission probability of each patient-HCW contact. During model experimentation, 500 replications will be carried out for each scenario with each lasting 415 days (50 days warm-up followed by 365 days for data collection). The average transmission ratio during the simulation period is used as the model response. Apart from the three experimental factors, all other input parameter values are set at default values according to Tables 6.2 and 7.9.

In the first scenario, the number of Type 1 HCWs (who only care for patients in the same unit) in each hospital unit changes from 5 to 15 (i.e., the total number of Type 1 HCWs in the hospital changes from 15 to 45). Consequently, the HCW-patient ratio changes from 1:5 to 3:5 assuming that on average 25 patients stay in each ward. Figure 7.11 shows the average transmission ratios of the hospital for different numbers of Type 1 HCWs. The figure demonstrates that as the number of Type 1 HCWs in each hospital unit increases from 5 to 15, the average transmission ratio decreases from around 0.16 to about 0.06. The results indicate that MRSA transmission ratio may be reduced if more Type 1 HCWs who only serve the patients in a single ward are provided.

A possible explanation for the relationship is that when more Type 1 HCWs are deployed in the ward, on average, the number of patients contacted by each Type 1 HCW is reduced (as the total number of contacts required by a patient is fixed) and therefore it is less likely that the HCW may act as a vector to spread MRSA in the ward. The fact that Type 1 HCWs only serve patients in a single hospital unit and can not transmit MRSA among different wards may also explain the result.

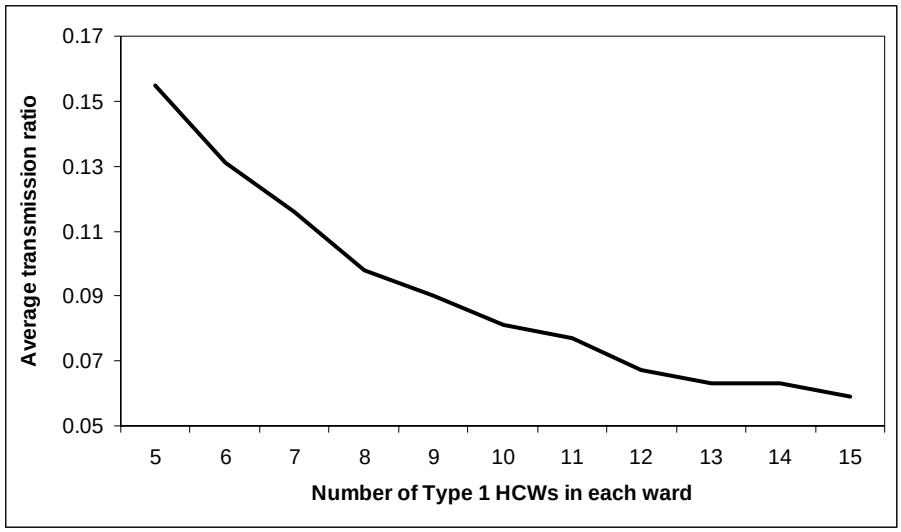

Figure 7.11 Average transmission ratios with different numbers of HCWs

For the second scenario, the hand-washing rate or decolonisation rate of HCWs changes from 10 times per day to 20 times per day. Figure 7.12 shows the average transmission ratios of the hospital under different hand-washing rates. The figure demonstrates that as the hand-washing rate increases from 10 to 20 times per day, the average hospital transmission decreases from around 0.23 to about 0.09. The results indicate that MRSA transmission ratio will be reduced if the HCWs can wash their hands more frequently to clear potential MRSA colonisation.

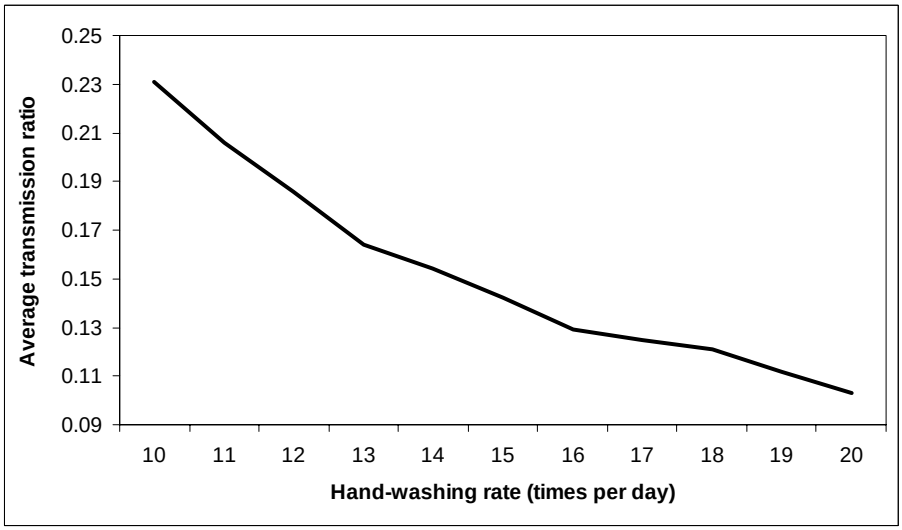

Figure 7.12 Average transmission ratios with different hand-washing rates

For the last scenario, the transmission probability of each patient-HCW contact changes from 0.05 to 0.15. Figure 7.13 shows the average transmission ratios of the hospital under different transmission probabilities. As expected, the figure

demonstrates that as the transmission probability increases from 0.05 to 0.15, the average hospital transmission increases sharply from around 0.04 to around 0.45. Compared to the first two scenarios tested, it appears that transmission probability is the most significant factor that affects the transmission dynamics of MRSA.

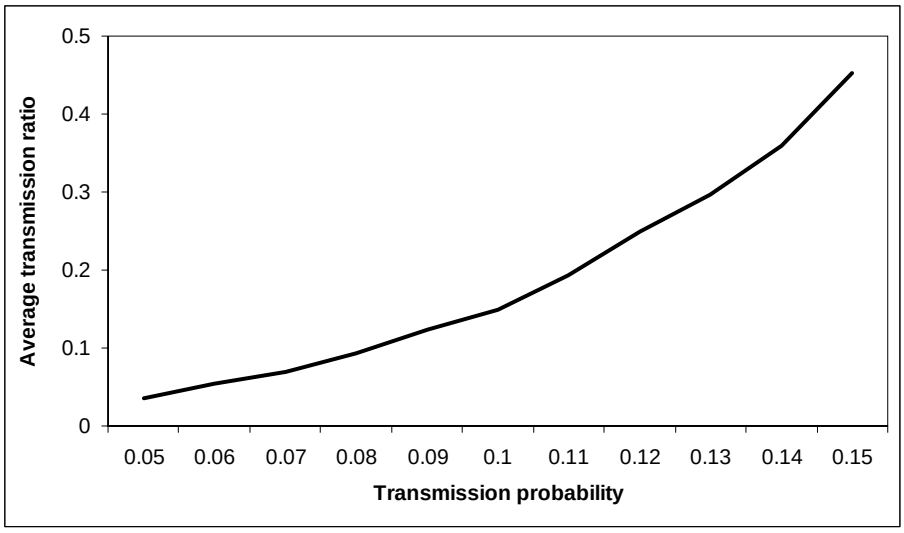

Figure 7.13 Average transmission ratios with different transmission probabilities

7.3.3 Conclusions

The purpose of the model extension is to demonstrate that ABS has the ability and flexibility to represent not only a single hospital unit and patient agents, but also a whole hospital with multiple units and HCW agents. In the extended model, the scaled-down hypothetical hospital has three hospital units and three types of agents, i.e., patients, Type 1 HCWs who only have contacts with patients in a single hospital unit and Type 2 HCWs who may have contacts with patients in the whole hospital. The transmission of MRSA in the extended model is represented by the host-vector model where each successful transmission between two patients is facilitated by a colonised HCW as the vector. The extended model is used to test some experimental factors which are not possible to evaluate in the original model. The results from the model experimentation demonstrate that MRSA transmission may be reduced with more Type 1 HCWs, more frequent hand-washing by HCWs, and lower transmission probabilities per contact.

The representation of multiple hospital units and HCWs as explicitly agents require dependable input data on the extent of transmission between different hospital units,

the colonisation status, hand-washing frequency and efficacy of HCWs, and the contact structure between HCWs and patients. In reality, it is difficult to obtain these data from observation. These issues may limit the practical application of this type of model, especially if the model is used to make quantitative predictions.

In future work, a full scale hospital can be represented with more hospital units, each of which may have different ward layout and different intervention policies. More proactive and intelligent behaviour rules of HCWs (e.g., reduced hand-washing frequency during busy time) in the extended model can also be added. The contact structure between patients and HCWs can be more realistically represented with the support of observed data. For example, each HCW may have a specific working shift and be responsible for a certain area of the ward; and some patients may require more HCW contacts than others.

7.4 Transmission Dynamics including the Community

7.4.1 Model Modifications

Many previous MRSA modelling studies have explicitly considered the community around, extend to, or served by the hospital and the interactions between the community and the hospital (Cooper *et al.* 2004; Robotham *et al.* 2006). However, these models are mainly mathematical compartmental models and the patients in the hospital are not represented as individuals or agents who have attributes, states and complex behaviour rules. In the model extension, the original MRSA model which only focuses on the transmission in a hospital ward will be extended to include the wider community and to represent the interactions between the hospital and the community. The purpose of the model extension is to demonstrate that ABS models, like mathematical compartmental models, can also efficiently represent the community and the wider and longer term transmission dynamics of HAIs beyond the boundary of the hospital.

By considering the wider community where the patients are admitted from and where they are discharged to, the proportion of patients who have already been colonised

with MRSA on admission (to the hospital ward) can be dynamically linked to the prevalence of MRSA in the community which, in turn, is partially dependent on the transmission dynamics of MRSA within the hospital ward (i.e., new secondary cases of MRSA in the hospital ward will increase the community reservoir of MRSA colonised patients, and successful decolonisation treatment in the hospital ward will reduce the size of the reservoir). Within the community, MRSA may be cleared with a natural clearance rate. Other assumptions of the extended model include:

- There is no MRSA transmission in the community which complies with the assumptions of previous models;
- The hospital may have several hospital wards (see Section 7.3), however, the extended model assumes that the scaled-down hospital has only one ward and, consequently, the size of the community is also scaled down proportionally;
- The total number of people in the community is constant and all hospital admissions come from the community and all discharged patients go back to the community;
- At the beginning of the simulation, the hospital ward is empty and a certain proportion of the people in the community is colonised with MRSA (the initial reservoir); and
- Every person in the community has equal probability of being admitted to the hospital ward which means, on average and in the long term, the proportion of colonised patients on admission equals to the proportion of colonised people in the community.

In the extended model, a person may be either in the hospital as a patient or in the community. If the person stays in the hospital, the main states and state transitions, the behaviour rules, and the way MRSA transmission is modelled will remain the same as the original model (see Chapter 4).

A person in the community has two states: colonised and susceptible. A colonised person in the community may change colonisation status to susceptible by natural clearance of MRSA defined by a parameter γ. Depending on the colonisation status of a patient when he/she is discharged from the hospital, the patient will return to the community as either colonised (in case the discharge colonisation status is colonised)

or susceptible (in case the discharge colonisation status is susceptible). When a person in the community is admitted to the hospital ward, depending on their colonisation status, the person will enter the hospital as either a colonised patient (if the community colonisation status is colonised) or a susceptible patient (if the community colonisation status is susceptible). A patient's main states and the state transitions of MRSA in the hospital ward and the community are illustrated in Figure 7.14.

The additional input parameters, their default values and the sources of the default values are shown in Table 7.10. The initial hospital ward is empty and the initial numbers of colonised and susceptible people in the community are assumed to be 70 and 1,500 respectively. It means the size of the scaled-down community is 1,570 and the initial prevalence of MRSA (i.e., the proportion of people colonised with MRSA) in the community is 4.7% which complies to the observed proportion of patients colonised with MRSA on admission in the case study (see Table 6.2). By assuming that every person in the community has an equal probability of being admitted to the hospital, the probability of a primary case admission in the hospital is $C/(C+S)$ and the probability of a non-primary case admission is $S/(C+S)$ where C and S represent the number of colonised and susceptible people in the community at the time of admission.

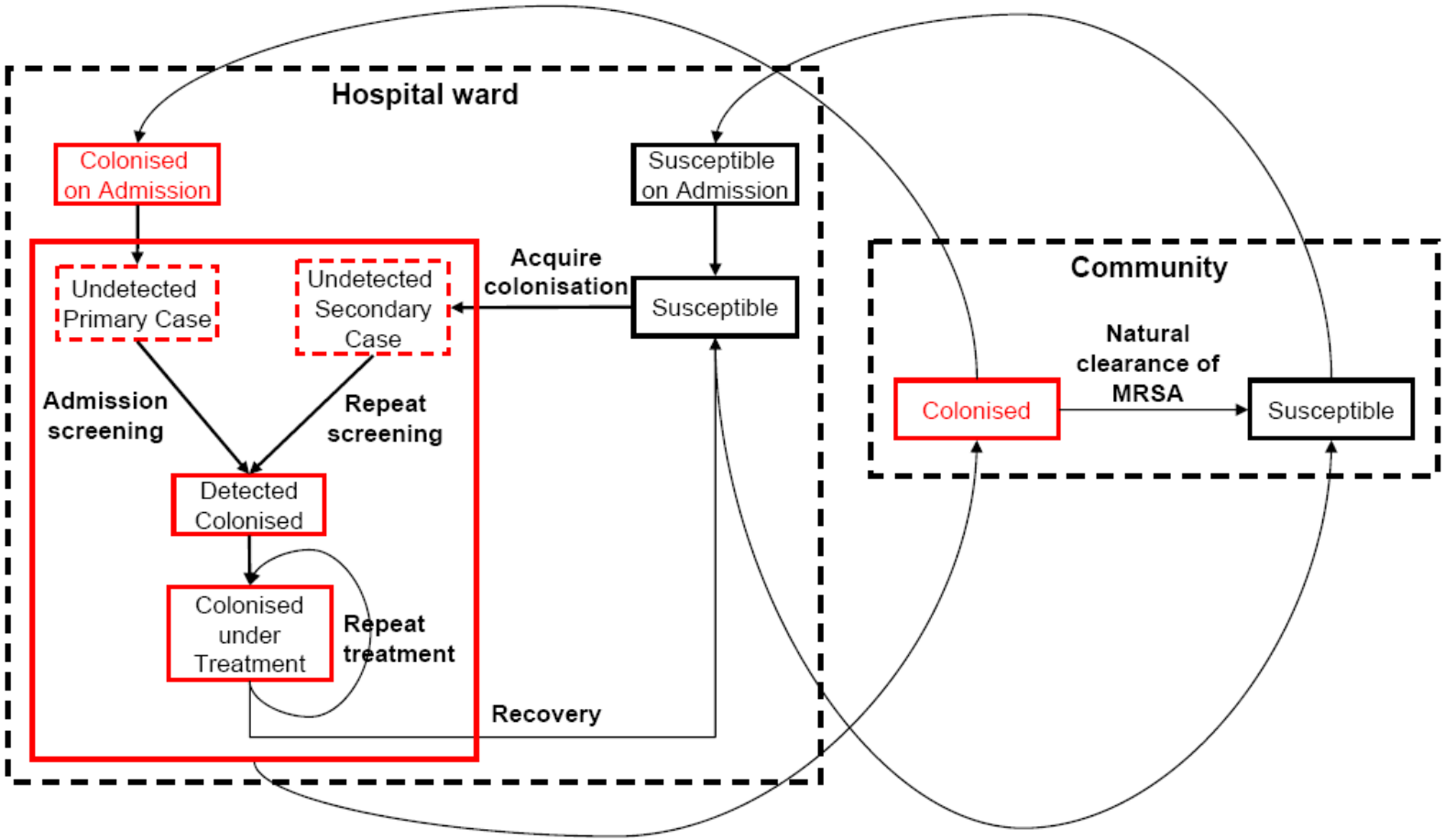

Figure 7.14 Patient main states and state transitions of MRSA in the hospital ward and the community

7.10 Additional model input parameters for model extension with community

Parameter	Value	Symbol	Source
Initial number of colonised people in the community	70	C_0	Assumption
Initial number of susceptible people in the community	1500	S_0	Assumption
Natural clearance rate of MRSA	0.0027	γ	Robotham *et al.* 2006

Due to the large number of people and the relatively simple states and state transitions of each person in the community, the numbers of colonised and susceptible people in the community are represented as two integer variables rather than fully-developed individual agents.

When a person in the community is admitted to the hospital, a new patient agent is created and enters the hospital, and either the number of colonised or the number of susceptible people in the community (depending on the colonisation status of the admitted patient) is reduced by one (i.e., *C* to *C-1* or *S* to *S-1*). When a patient is discharged from the hospital, the patient agent is disposed of and leaves the hospital, and either the number of colonised or the number of susceptible people in the community (depending on the colonisation status of the discharged patient) is increased by one (i.e., *C* to *C+1* or *S* to *S+1*).

Regarding the natural clearance of MRSA in the community, for each time interval (i.e., one day), the expected number of people in the community that should clear MRSA is calculated by multiplying the number of colonised people in the community at the time of evaluation and the natural clearance rate, or $\gamma \cdot C$. Then, by random sampling, a Poisson distribution (where the mean of the distribution is set at $\gamma \cdot C$ during the time interval) is used to decide the number of people that actually cleared MRSA during the time interval. Essentially, people in the community are grouped into two homogeneous compartments in the extended model and the method has been applied by previous mathematical compartmental models (Cooper *et al.* 2004; Robotham *et al.* 2006).

7.4.2 Model Experimentation

For each scenario during the model experimentation, the extended model is run for 10 years (3650 days or about 521 weeks) to demonstrate the long term trend of MRSA

prevalence in the community. The community prevalence, which is the proportion of people in the community that are colonised with MRSA, is less subject to randomness and chance effects compared to the hospital prevalence due to the relatively large sample size in the community. The community prevalence is collected every week during the 10-year simulation period. Three scenarios are constructed to explore the long term impact of MRSA interventions within the hospital on the community prevalence.

In the first scenario, only the admission screening test is performed in the hospital and there is no repeat screening test. The interventions of isolation and decolonisation treatment are still in place but will only apply to primary case patients since secondary case patients can no longer be detected (by repeat screening tests). The extended model is run for 10 replications with each lasting for 10 years. The changes of community prevalence are shown in Figure 7.15. The ten thin lines represent the community prevalence of each replication and the thick line represents the average change of the community prevalence based on all replications. The average trend line shows clearly a steady increase in the community MRSA prevalence in the next 10 years (from around 4% to around 11%). It indicates that the hospital intervention policy has failed to contain MRSA and the community reservoir gradually builds up during the simulated years.

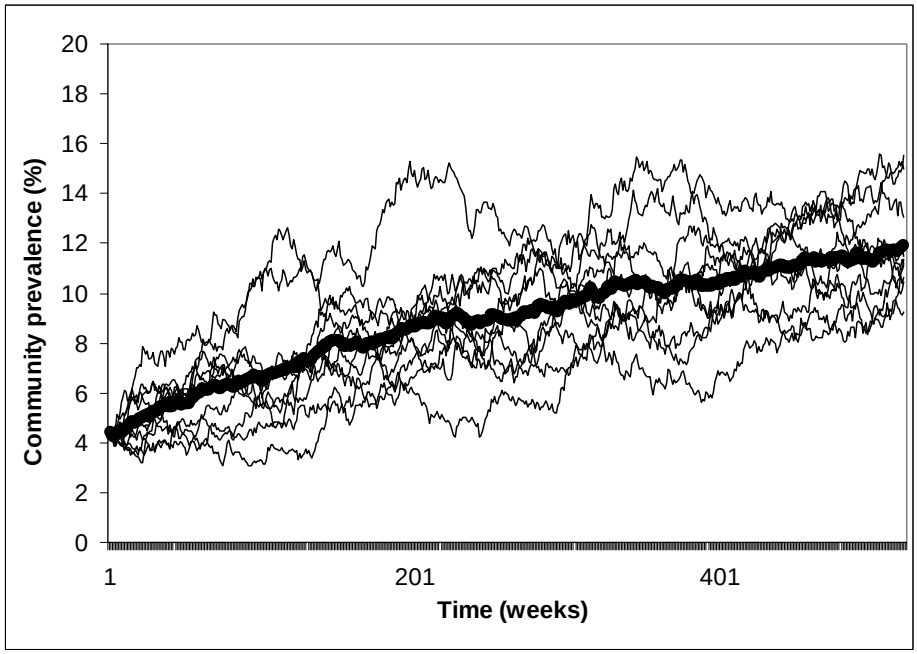

Figure 7.15 Change of weekly MRSA prevalence in the community (scenario 1)

In the second scenario, the intervention policies adopted by the hospital are the same as the hypothetical test ward in Chapter 6 which means not only admission screening test but also four day repeat screening test are performed. Since repeat screening tests are carried out, isolation and decolonisation treatment may now apply to both primary case and secondary case patients. The individual and the average changes (10 thin lines and one thick line) of weekly community prevalence during the next 10 years are shown in Figure 7.16. The average trend line shows that the community prevalence of MRSA is fairly stable at the initial level for a few years and then slightly decreases to about 2.5% by the end of year 10. It indicates that, in the long term, the intervention policy in the hospital may maintain or slightly reduce the MRSA prevalence in the community.

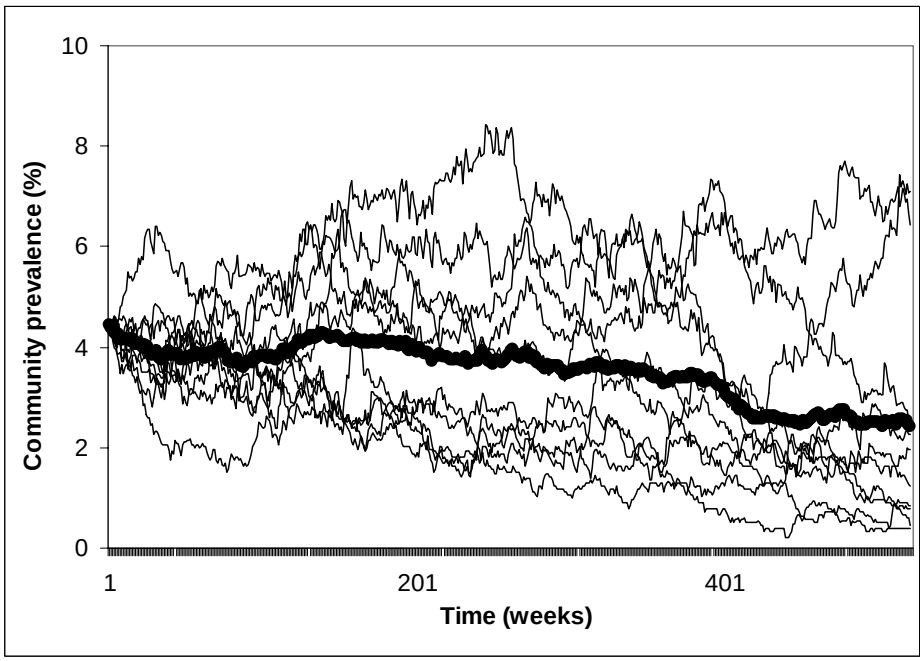

Figure 7.16 Change of weekly MRSA prevalence in the community (scenario 2)

In the last scenario, the hospital adopts more aggressive intervention policies. Compared to the second scenario, the interval of the repeat screening test is reduced from four days to only one day while the rest of the interventions remain unchanged. The individual and the average changes of weekly community prevalence during the next 10 years are shown in Figure 7.17. The average trend line shows clearly that the community prevalence of MRSA steadily decreass in the next 10 years (from around 4 percent to less than 0.15%). It is a clear indication that the aggressive intervention

policy will, on average, significantly reduce the MRSA prevalence in the community in the next few years.

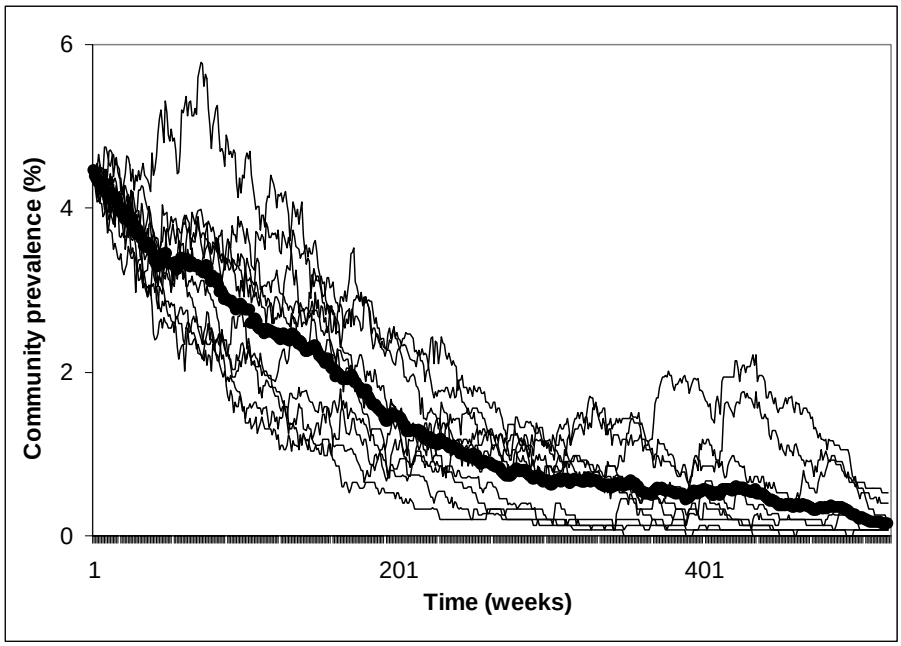

Figure 7.17 Change of weekly MRSA prevalence in the community (scenario 3)

Figure 7.18 compares the average changes of the community MRSA prevalence under the three scenarios tested. The diagram demonstrates how different MRSA intervention policies may affect the community prevalence of MRSA in the long term.

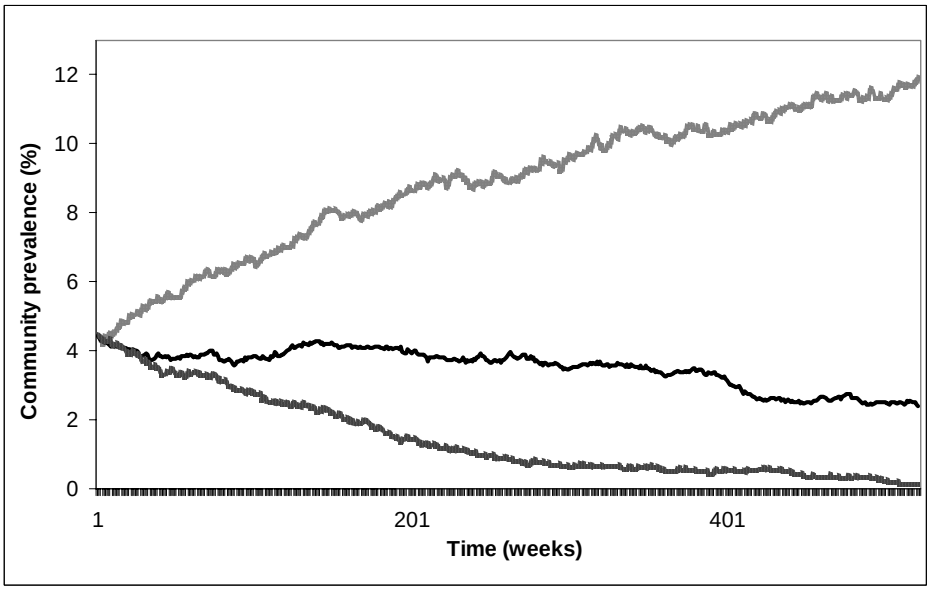

Figure 7.18 Comparison of the change of weekly MRSA prevalence in the community with different hospital interventions

7.4.3 Conclusions

Previous mathematical compartmental models have studied the wider transmission dynamics of MRSA including both the hospital and its wider community. The purpose of the model extension is to demonstrate that ABS can also efficiently incorporate the community population and capture the long-term feedback relationship between the hospital and the community. In the extended model, due to the large size of the community, people in the community are grouped into two compartments and represented as integer variables; while patients in the hospital ward are still represented as fully-developed agents who have multiple attributes and states, and complex behaviour rules. The extended model demonstrates that MRSA intervention policies adopted by the hospital may have significant long term impacts on the community MRSA prevalence. The limited model experimentation indicates that it is possible to reduce MRSA prevalence in the wider community in the long term by consistently implementing aggressive intervention policies within the hospital. All experimental results from the extended model comply with the results from previous models.

The hospital and the community are scaled-down in the extended model. It might be worthwhile to represent a complete hospital with many different hospital wards and the overall community of the hospital. People in the community may have more attributes and states to represent different readmission rates to the hospital. With the support of clinical evidence, transmission of MRSA in the community may also be embedded. Furthermore, the size of the community may be dynamic and people (colonised or susceptible) may move between different communities. Despite of the limitations, the model extension demonstrates the ability and flexibility of ABS to model the wider transmission dynamics of MRSA when hospital community is included.

7.5 Summary

Three model extension exercises have demonstrated the flexibility, ability and potential of ABS to model HAIs in different situations. The original MRSA model is extended to consider two competitive infections (i.e., MRSA and *C. difficile*), to

include HCW agents and represent the transmission of MRSA among multiple hospital units, and to include the wider community population. For each model extension, the modifications to the original model are discussed regarding additional model assumptions, structures and parameters. Various model experimentations are also performed to gain new insights that can not be studied by the original MRSA model. The extended models are not configured with observed data so it has limited value in terms of recommending effective intervention policies.

Chapter 8

Conclusions

8.1 Introduction

This chapter summarises the work performed in the thesis. It outlines the problem situation and literature review of the subject and revisits the research objectives and questions. Then, the chapter reflects how each research objective has been met, and discusses whether and to what extent each research question has been answered. Finally, the limitations of the work are discussed and the future work is proposed.

8.2 Problem Situation and Literature Review

HAIs, such as MRSA and *C. difficile*, can lead to severe morbidity and mortality among hospital patients and place heavy burdens on healthcare resources. Hospitals and public health authorities around the world are trying to find the most cost-effective strategies and policies to prevent and control HAIs. Popular intervention policies to prevent and control HAIs include the Search-and-Destroy strategy (e.g., pre-emptive screening tests followed by isolation and decolonisation treatment) and some general policies such as hand-washing by HCWs, ward cleaning and education of hospital staff. Compared to infectious diseases mainly transmitted in the community, HAIs have some distinctive features including rapid patient turnover, small patient population size, the existence of asymptomatic carriers and the endemicity of some HAIs in the hospital setting. These special features may affect the choice of modelling methods to describe and study HAIs.

Many previous studies have applied different types of modelling techniques to study the transmission dynamics of infectious diseases in the hospital setting. Most of the studies used mathematical compartmental models in which patients or HCWs are

grouped into different compartments depending on the colonisation status or other risk factors. Within each compartment, patients and HCWs do not have individual identities and are assumed to be homogeneous. Early compartmental models were often solved deterministically by analytical methods, while recent models have been increasingly evaluated stochastically through the Monte Carlo random sampling technique. There were a few existing studies to investigate HAIs by individual-based models in which each patient or HCW is explicitly represented and the transmission of the infectious disease is modelled on an individual basis. However, these models have not explored the full potential and flexibility provided by the individual-based approach and still retained many restrictive assumptions of mathematical models such as exponentially distributed lengths of stay and full ward occupancy. The scope of previous models ranged from a single hospital unit to the whole hospital together with its community.

ABS is a bottom-up rather than top-down modelling approach which means the overall system behaviour emerges from and is determined by locally defined agents who interact with other agents and with the system environment. An agent, ranging from a simple reactive agent to a sophisticated intelligent and adaptive agent, may have various attributes and multiple states associated with it, and behaviour rules to govern its state transitions. ABS has been widely applied to many domains from business and management to social science. A few studies have applied ABS to model the transmission of community infectious diseases. However, there has been no previous research to apply ABS to study the transmission dynamics of HAIs.

The review of existing modelling studies of HAIs and the introduction of ABS provide the research opportunity to study HAIs using the technique of ABS. To fulfil this general objective, the thesis aims to investigate the feasibility and value of using ABS to provide a flexible and robust modelling approach to support the modelling and management of HAIs, to provide a general framework of applying ABS to the modelling and management of HAIs, to test and validate the use of ABS on a MRSA study, and to quantify the effectiveness and test the robustness of various MRSA intervention polices and indicate the best practices to the management of MRSA in the hospital setting.

8.3 Summary of Research

8.3.1 Agent-based Simulation as a Decision Supporting Tool to the Modelling and Management of Hospital-acquired Infections

The first research objective is to investigate the value and feasibility of using ABS to provide a robust and flexible modelling approach to support the modelling and management of HAIs. The corresponding research questions are whether, why and when ABS is a useful technique to the modelling and management of HAIs.

In order to facilitate the discussion of advantages of ABS relative to other modelling methods, a taxonomy of the potential modelling techniques that can be applied to study HAIs was proposed in Chapter 3. In the taxonomy, modelling techniques were classified as either cohort/aggregate level models where patients were grouped into different compartments or individual level models where each patient was explicitly represented and may have heterogeneous attributes. Cohort/aggregate models include mathematical compartmental models, Markov models and SD models. They can be deterministic or stochastic and, in both cases, may be solved analytically or evaluated numerically. Individual level models include ABS, DES and general individual-based models. Although they have distinctive features, they do share some properties (e.g., patients are represented as heterogeneous individuals), and they may have overlaps with each other (e.g., ABS and DES may both have the capability of event-scheduling). Most individual level models are stochastic in nature and are evaluated numerically through computer simulation.

Based on the proposed taxonomy, the advantages and disadvantages of ABS relative to cohort/aggregate models and other types of individual-based models were discussed and the justification of using ABS was explained. The relative advantages of ABS (and other types of individual-based models) relative to cohort/aggregate models include the ability to represent individual patients and HCWs, and their attributes, risk factors and states; to represent spatial location and movements; to relax restrictive assumptions; to represent sufficient detail and complexity; to make reliable quantitative predictions; to be transparent and easily understood; and to collect individual-based statistics. The relative disadvantages of ABS compared to

cohort/aggregate models include the absence of rigorous mathematical expressions, the fact that they are less parsimonious and data demanding, more time is required for model coding and their relatively slow running speed.

ABS and DES are both individual-based simulation techniques and they have many similarities. In order to compare the two methods in the context of HAI modelling, their differences were investigated in detail (see Section 3.4.2). Compared to DES, the relative advantages of ABS are that it is a more natural choice to represent patients and infection transmission process, a more powerful tool to represent patient behaviour rules, patient spatial location and movements and multiple concurrent state changes, and is more transparent. The relative disadvantages of ABS include fewer and less user-friendly software packages and the fact that it is less effective in representing queuing systems.

Apart from the theoretical analysis, the justification of applying ABS to the study of HAIs may be further strengthened by building the same prototype model using software packages of different modelling methods such as ABS, DES and system dynamics. The process of the building of the models can then be reflected and compared, and the model results can be compared. The exercises may require considerable extra time and effort, but could provide more detailed insights into the advantages and disadvantages of ABS relative to other modelling methods. The conclusions from the theoretical comparisons between ABS and other methods may also be tested by the modelling exercises.

The rest of the thesis discussed the main methodological issues and described a framework of applying ABS on HAI modelling. A MRSA case study model was later developed and validated based on the empirical study. The MRSA model was further extended to include a competitive infection, multiple hospital units and HCW agents, and the wider community of the hospital. These discussions further demonstrate the feasibility and flexibility of applying ABS to describe and study HAIs. In short, the thesis has investigated and demonstrated the value and feasibility of using ABS as a robust and flexible modelling approach to the support of modelling and management of HAIs.

8.3.2 Application of Agent-based Simulation to the Modelling and Management of Hospital-acquired Infections

The second research objective is to provide a general framework of applying ABS to the modelling and management of HAIs and to test and validate the use of ABS on a MRSA study. The corresponding research questions are how ABS can be applied as a general framework to the modelling and management of HAIs and how ABS can be applied to model a MRSA study and be properly validated. The research objective and questions are mainly dealt with in the methodology, model description and model validation chapters (Chapters 3, 4 and 5).

General Framework

The aim of the methodology chapter is to address the key methodological issues and set out a framework of applying ABS to the modelling and management of HAIs. The ABS model adopts a hierarchical structure which consists of two levels. The higher level of the model structure represents the system environment (e.g., the whole hospital or a specific hospital ward) where the patient agents stay, and the lower level of the model represents individual patient or HCW agents and how agents interact with other agents and with the system environment.

In the proposed framework, individual patient agents may have different attributes (e.g., age, gender, vulnerability, infectivity), multiple concurrent streams of states (e.g., states regarding colonisation status, detection status and location) and, more importantly, behaviour rules to govern the state transitions (e.g., rules for infection transmission). Due to the application of ABS, patients' lengths of stay can be sampled from any types of parametric or empirical distribution, and may depend on the characteristics of the patient; patient may have multiple concurrent state changes; and ward occupancy can be determined by model dynamics and bed availability and may fall below 100%.

The hierarchical overall model structure and the representation of patient agents by attributes, states and behaviour rules are typical characteristics of ABS models in general. The framework is a natural way to represent the transmission of HAIs in the hospital setting. It also brings the flexibility and advantages provided by the agent-based approach.

Representing the infection transmission process is another important methodological issue of modelling HAIs which was discussed in detail in the methodology chapter. Three different ways to model infection transmission were discussed: the host-vector model structure, the classical mass action assumption, and the proposed pairwise action assumption which modifies the mass action assumption to suit individually represented patients (see Section 3.7).

As an individual-based modelling approach, ABS model is able to represent distinctive characteristics of each patient which may affect the chance of the patient acquiring HAIs (if the patient is susceptible) or transmitting the HAIs (if the patient is colonised). Ideally, the chosen method to represent infection transmission should be able to incorporate such individual variability so that the advantage of ABS can be realised. Among the three methods discussed, the host-vector model structure and the pairwise mass action assumption can both allow for patient heterogeneity, with the former suitable when HCWs or other vectors are explicitly modelled and the latter appropriate when only patients are represented. The pairwise action assumption was later applied to the empirical MRSA model.

Individual patients' vulnerability and infectivity are relatively easy to be represented by the transmission probability equations. The relative adjacencies between patients, which may also affect transmission probability, are not straightforward to be embedded in the model. It may not be feasible to model the exact distance between each pair of patients in the model. Instead, it is recommended that the ward bay location of each patient is kept so that the model knows whether two patients are in the same local environment at any time. The model can then treat global and local interactions differently. The way to represent patient locations and how relative adjacency between patients may affect transmission probability may be improved by using other methods. However, it is important that the location information is reflected by the ABS model.

A combination of an event-driven and time-slicing time advance mechanisms are adopted. Event-driven method should be used for most modelled activities since it is efficient and time between events can be sampled from any types of continuous

distributions. However, to avoid potential problems caused by scheduling future events of susceptible patients concerning acquiring colonisation, the infection transmission process is modelled using the time-slicing mechanism (see Section 3.7.5).

The experimental factors and model responses, and the choice of experimental design methods were also discussed as part of the general modelling framework.

MRSA Case Study

Based on the framework proposed in the methodology chapter, an ABS model to study the transmission of MRSA in the hospital setting was developed in Chapter 5. The building of the model was originally part of a MRSA research project funded by the Department of Health and carried out in Birmingham Heartland Hospital (Hardy *et al.* 2007). The scope of the ABS model is a single hospital ward divided into bays, with some isolation rooms. The only type of agent represented by the model is the patient.

The model tries to represent the details of the corresponding empirical study. The wards in the model have the same layout as in the actual hospital and most patient characteristics in the model are based on empirical patient-level data collected during the study. The key interventions and operation rules that were implemented in the study hospital were all incorporated into the model. The proposed MRSA model allows many intervention policies and influencing factors to be tested, some of which have not been represented before such as test turnaround time, screening strategy, and the proportion of transmission coming from the bay.

Many detailed model dynamics, which have not been represented before, have been captured by the MRSA model. For example, the model is able to explicitly represent the delay between the time when the screening sample is taken and when the test result is reported. The model may be further improved by adding more detailed model dynamics that are relevant to the transmission dynamics of MRSA. For example, the accuracy of the screening tests can be allowed for so that tests of different sensitivity and specificity can be compared. However, such improvement will require additional model inputs and may change the model structure.

The MRSA model was validated against observation (including the transmission ratio, the number of secondary cases, and the time to detection) applying a calibration-validation process where the parameter to be calibrated is the transmission coefficient (see Section 5.3.1). It is possible to improve model validation and gain more confidence on the model by comparing additional model responses with the corresponding observations if empirical data are available.

8.3.3 MRSA Infection Control in the Hospital

The last research objective is to quantify the effectiveness and test the robustness of various MRSA intervention policies and indicate the best practices to the management of MRSA in the hospital setting. The corresponding research questions are how to quantify the effectiveness of various MRSA intervention policies, how robust are these intervention policies considering various influencing factors, and what are the best practices for the management of MRSA in the hospital setting. The model experimentation chapter (Chapter 6) aims to answer these questions.

After reasonable confidence in the model was gained through validation, the model was systematically explored by two formal experimental design methods: fractional factorial design with resolution V and the response surface design. The experimental factors tested through model experimentation, in the order of controllability, include test turnaround time, screening strategy, number of isolation beds, effectiveness of decolonisation treatment, transmission coefficient, proportion of transmission within bay, average length of stay and endemic setting. It is the first time a number of MRSA interventions (e.g., test turnaround time) have been systematically studied by formal experimental design methods.

The main experimental design method is the fractional factorial design where each experimental factor was set on two levels, base level and alternative level, and the main effects and two-way interaction effects of the eight experimental factors were systematically evaluated. In order to reduce the number of design points and consequently computational time and efforts, a fractional factorial design with resolution V is chosen over the full factorial design (see Section 6.2.1).

Due to the limitations of the factorial design (e.g., linearity assumption), a response surface design was applied to explore the non-linear effects of two experimental factors on the model response, and the non-linear interactions between the two factors. Response surface design experiments were performed between the screening strategy and the average length of stay, the test turnaround time and the average length of stay, and the number of isolation beds and the proportion of transmission coming within bay.

The practical implications and indications to the hospital management were summarised in Section 6.7.1. The conclusions from the model experiments can help the hospital to better manage the prevention and control of MRSA. The effectiveness of three intervention policies (i.e. the test turnaround time, the screening strategy and the number of isolation beds) and their interactions with other factors should be of particular interest to the hospital management as the hospital has much control over these policies. Among the interventions tested, test turnaround time and screening strategy have not been systematically investigated in such a detail by previous modelling studies. The research gives strong support to the introduction of rapid screening tests and more frequent screening tests. Providing more isolation facilities is also shown to be an effective policy; however, its effectiveness is highly dependent on how effective the isolation is.

8.4 Limitations

The thesis proposed a general framework of applying ABS model to the modelling and management of HAIs. In theory, the framework applies to any type of HAIs and any hospital environment. However the case study which implemented the framework is based on an empirical MRSA study in a UK hospital and all hospital wards involved in the research project are surgical wards. Therefore, the hypothetical test ward used for model experimentation may not represent hospitals outside the UK or hospital units other than surgical wards. However, the main experimental factors were systematically tested on difference levels (i.e., base and alternative levels during fractional factorial design and more levels during response surface design) during model experimentation, which means the experimentation has considered different

scenarios other than the default settings of the test ward. As a result, the conclusions drawn from the model experimentation should be able to apply to other types of hospital units and hospitals outside the UK.

In the proposed framework, ABS model could either represent just patient agents, or both patient and HCW agents. Due to the lack of understanding of the underlying transmission routes and the lack of reliable observed data, the current MRSA model only explicitly considers patient agents. As a result, some intervention policies, such as hand-washing frequency and compliance rate, HCW allocation rules and HCW-patient ratio can not be explicitly and easily represented and tested by the MRSA model. Preliminary attempts have been made to extend the MRSA case study model to include multiple hospital units and HCW agents (see Section 7.3). In the extended model, it is assumed that the only transmission route is cross transmission by transiently colonised HCWs who may either serve a single hospital unit or serve multiple hospital units. The extended model was not configured with and validated against observed data and no systematically model experimentation was carried out. Another limitation of the extended model is that the behaviour rules of HCW agents have not been fully explored by the ABS approach. The model extension also demonstrated the additional data requirements when HCW agents are modelled. Such requirements may prohibit the use of the patient-HCW model structure.

The original MRSA model which only focuses on a single HAI within a hospital ward was also extended to include a competitive infection (i.e., *C. difficile*), and to include the wider community (see Section 7.2 and 7.4). However, the modifications to the original model were moderate without the backing of observed data and without formal model validation and experimentation. The model extension attempt to include the wider community also demonstrated the potential problem of apply the ABS model when large number of individuals need to be represented (e.g., the community). The extended model got over this problem by representing the number of people in the community as integer variables while retaining agent structure within the hospital. Another limitation of the extended model is that no transmission is assumed within the community.

The proposed MRSA model focused on the effectiveness of different intervention policies only from the perspective of clinical benefits of reduced MRSA transmission ratio or reduced number of MRSA secondary cases. In reality, hospital management decisions or, in general, decisions made by public health authorities, such as the NHS and the National Institute of Clinical Excellence in the UK, compare alternative intervention policies not only on the ground of clinical effectiveness but also on the ground of costs associated with the policy. For example, the experimental results indicated that a screening test with shorter test turnaround time and more frequent screening tests will significantly reduce the transmission ratio of MRSA in the hospital setting. The conclusion is robust and convincing on the grounds of clinical effects; however, faster and more frequent screening tests are associated with a higher cost than the slower convention culture tests and less frequent screening tests. In reality, the clinical benefits and the corresponding costs have to be balanced so that an economically feasible management decision can be made.

8.5 Future Work

Firstly, future work may be carried out to configure the current MRSA model with observed data from other empirical MRSA studies that are based on non-UK hospital or other types of hospital ward other than surgical wards. It is likely that a different hypothetical test ward may be created with a different estimated transmission coefficient. Similar model experimentations (e.g., factorial design and response surface design) can be carried out and the conclusions from the experiments can be compared with the conclusions from this research. Although the configuration of the test ward and the transmission coefficient may be different, it is expected that general conclusions about the effectiveness of different intervention policies should be similar to this research.

In future work, if reliable data about the contacts between HCWs and patients and the colonisation status of the HCWs are available, the current MRSA model may be modified to explicitly represent HCWs. In the modified model, the hand-washing frequency and compliance rate may be embedded in the model as intervention policies. With the support of reliable clinical evidence and observed data, the model may also

embed other important factors which may significantly affect MRSA transmission such as the accuracy of the screening test (e.g., the sensitivity and specificity).

With the support of empirical data, the transmission dynamics of two competitive infections and the transmission dynamics among multiple hospital units can be represented in more detail than what has been done for the extensions of the MRSA model. For example, interactions between the two competitive infections may be represented by the model. Regarding the model extension to include the wider community, future work may represent the wider transmission dynamics of MRSA in a region which consists of one or more hospitals (each with multiple hospital units) and the overall community. MRSA transmission within the community may be modelled with the support of clinical evidence. People in the community can be further classified not only by the MRSA colonisation status, but also by other factors such as readmission rate to the hospital. The community size may also be dynamic considering immigration and emigration.

Another important and practical future work is to extend the current research by including the cost-effectiveness analysis of various intervention policies. With the help of cost-effectiveness analysis, hospital management and public health authorities can make better informed decisions as to whether and how to implement specific intervention policies.

One of the special features of ABS is to represent intelligent agents who can make active decisions. In future work, the patient and HCW agents (if they are represented by the model), especially the HCW agents, may be designed to be more active and intelligent by embedding more flexible and adaptive behaviour rules that represent the real decision making process of the real world. For example, when the workload increases (e.g., hospital ward occupancy is high), HCWs may wash their hands less frequently; and when a series of secondary MRSA transmissions are detected, the hospital may enforce more aggressive short-term intervention policies such as temporarily ward closure, strict hand-washing and contact precaution protocols. The future work can further demonstrate that ABS is a powerful and flexible method to model HAIs.

8.6 Summary

The thesis represents the first attempt to apply the modelling method of ABS to study the transmission dynamics and intervention policies of HAIs in general and MRSA in particular. Based on the proposed taxonomy of potential methods for modelling HAIs, the relative advantages and disadvantages of ABS compared to other methods, in particular mathematical compartmental models and DES, are investigated. The comparison provides a theoretical justification to the application of ABS on modelling HAIs.

The main methodological issues of using ABS to study HAIs are discussed, including the representation of patient agents and the modelling of the infection transmission process. In an ABS model, the lengths of stay of patients can be sampled from any types of parametric or empirical distribution, the patient may have multiple concurrent streams of state changes, and the ward occupancy may vary and fall below 100%. Depending on whether vectors (e.g., HCWs) are explicitly represented, an ABS model can use either a host-vector model structure or mass action assumption to model infection transmission. Pairwise action assumption, which is modified from mass action assumption, is proposed to suit the needs of ABS models. The assumption allows for individual vulnerability and infectivity, and the spatial adjacency in the transmission probability equations. A general framework of how ABS can be applied to model and study various types of HAIs are proposed. The framework not only guides the building of the empirical MRSA model in the thesis, but also is design in a way that can be universally applicable to study any types of infectious disease in the hospital setting (e.g., *C. difficile*).

The building of the MRSA model and the subsequently validation of the model are based on an empirical research study carried out in the Birmingham Heartlands Hospital. Compared to previous models, the MRSA model is more realistic and captures the recent development in the clinical studies of MRSA. In the model, each patient agent has unique vulnerability and infectivity. The hospital unit is divided into different ward bays and isolation rooms and patient may move among these locations. The occupancy of the unit may vary over time and the patient's length of stay is sampled from empirical or gamma distribution. The model has embedded the

turnaround time and the frequency of the screening tests, and the duration, the effectiveness and the success rate of decolonisation treatment. These intervention policies have been evaluated by clinical study in recent years but have not been investigated by previous modelling studies. The MRSA model is configured with and validated against observed data.

Once a reasonable level of confidence has been placed in the model through the validation process, formal experimental design methods, including fractional factorial design and response surface design, are applied to systematically investigate the effectiveness of various intervention policies and potential interactions among different polices. The model results strongly support the use of rapid screening tests to reduce MRSA transmission in the hospital setting. The model results show that reducing the test turnaround time can result in a significant reduction of MRSA transmission. Regarding screening strategies, admission screening is found to be very effective to curb MRSA transmission. When admission screening is in place, adding repeat screening may further reduce transmission; however, the effectiveness of more frequent repeat screening depends on patients' lengths of stay. Isolating MRSA colonised patients is also found to be an effective policy. However, the effectiveness of isolation is significantly dependent on how effective isolation can prevent the transmission to and from the isolation facility. These implications and indications can help hospitals and public health authorities to effectively manage MRSA in the hospital setting.

Finally, the MRSA model is extended to explore a series of situations that have not been considered by the original model. The model is extended to include a competitive infection, *C. difficile*, to include multiple hospital units and HCWs, and to include the wider community. The model extensions further demonstrate the flexibility and benefits of applying ABS on HAI modelling.

Appendix A

Representation of other Types of Agents

Apart from patient agents, other types of agents may need to be represented in the ABS model. These agents may include HCWs and other human (e.g., visitors) or non-human (e.g., common toilets) objects which are vectors for the transmission of HAIs.

A.1 Representation of HCW Agents

Transiently or permanently colonised HCWs are thought to be the main vector for the transmission of many infectious diseases in the hospital setting (Cooper *et al.* 1999; Bootsma *et al.* 2006). Some, but not all, previous HAI studies explicitly have represented HCWs in the models. It is worthwhile to represent HCW agents in the model if (1) the assumption that the HCW is an important vector is justified for the infectious disease under study, and (2) data regarding the contact frequency and structure between HCWs and patients, the probability of transmission per contact, hand-washing rate/compliance and the efficacy of hand-washing in eradicating the pathogen are available through observation, previous studies or reasonable assumption.

Like patient agents, a HCW agent will have attributes, states and behaviour rules and collectively they define the HCW agent. The attributes of a HCW that may potentially affect or be associated with infection transmissions may include:

- The schedule of the HCW's working shift such as the starting and finishing time of each shift;
- The number of patients or the areas of the hospital or hospital unit that the HCW is responsible for;
- The contact pattern with patients such as the frequency and the nature of the contact (e.g., high risk contact involving patient's body fluid);
- The hand-washing rate/compliance and the efficacy of the hand-washing; and

- Attributes that may affect HCW's vulnerability and infectivity.

The states of a HCW are normally simpler than that of the patients in a HAI model. These states can be classified into the following categories of state changes:

- Colonisation status: the HCW in a HAI model normally has only two states regarding colonisation status which are susceptible and colonised; and
- Working status: if working shift is represented, the HCW can have two states representing the working status which are at work and off work.

Potential behaviour rules which govern how HCW's state changes from one to another; and how the HCW interacts with patient agents and with the environment can be classified into the following categories:

- Colonisation/decolonisation rules. These rules describe how the HCW's state changes from susceptible to colonised and from colonised to susceptible (e.g., via hand-washing);
- Rules of transmitting infectious disease to susceptible patients. These rules describe how a colonised HCW transmits the pathogen to susceptible patients; and
- Contact rules between HCWs and patients. These rules describe the contact structure and frequency between HCWs and patients.

The behaviour rules of HCWs are not necessarily reactive but can be more flexible and proactive since HCWs, unlike patients, may control their own behaviours and not necessarily comply with regulations and principles (e.g., hand-washing rules and barrier precautions). Depending on the dynamic environment setting, HCWs may vary their behaviours accordingly (e.g., when the workload is increased, it is less likely that HCWs will comply with hand-washing rules). Therefore, if HCWs are explicitly represented in the ABS model, proactive and adaptive rules may be considered when designing their behaviour rules.

A.2 Representation of Other Types of Agents

Besides patients and HCWs, other types of agents may also be incorporated into the model if they are assumed to be important vectors (e.g., visitors) for the transmission

of the pathogen under study and if data are readily available. The representation of these types of agents is similar but normally simpler than the representation of HCW agents.

Appendix B

Preliminary Comparison with Previous Models

B.1 Introduction

Before the full-scale ABS model was built, two preliminary tests were performed to use ABS models to replicate the assumptions and results of two previous MRSA studies adopting mathematical compartmental models. ABS models were built based on the same assumptions and were configured with same data in these studies. Then, the results from the ABS models are compared with the results from the previous studies.

The main purpose of the pilot tests was to demonstrate that ABS can be at least as good as the existing mathematical compartmental models to describe and study MRSA transmission dynamics even without further exploring the advantages and distinctive features of ABS. Another aim was to test and get familiar with the software, Anylogic®, before it was used to develop the models for the research study.

B.2 Test Agent-based Simulation Model on Previous Studies – Part I

B.2.1 Assumptions and Input Parameters

The first model to be tested by ABS model is proposed by Cooper *et al.* (1999). The mathematical compartmental model focused on a single hospital unit, explicitly considered both patients and HCWs and classified each of them as either susceptible or colonised. The main assumptions of the model include:

- Only a single hospital unit is modelled, the dynamics between different wards within the hospital and the dynamics between the hospital and the community are ignored;
- Patient-to-patient cross transmission via transiently colonised HCWs is assumed to be the only transmission route of MRSA;

- 100% bed occupancy and constant numbers of patients and HCWs;
- Detection of positive patients is assumed to be a random process with a fixed rate;
- Identified positive patients are assumed to be removed from the ward immediately and will no longer transmit the pathogen;
- Homogeneous patients and HCWs regarding vulnerability, infectivity and other risk factors;
- Transiently colonised HCWs can get rid of MRSA through hand-washing with 100% efficacy;
- Colonised patients will not be decolonised during the hospital stay.

Figure B.1 shows the flow diagram of the model and Table B.1 shows the main input parameters and their default values taken by the model.

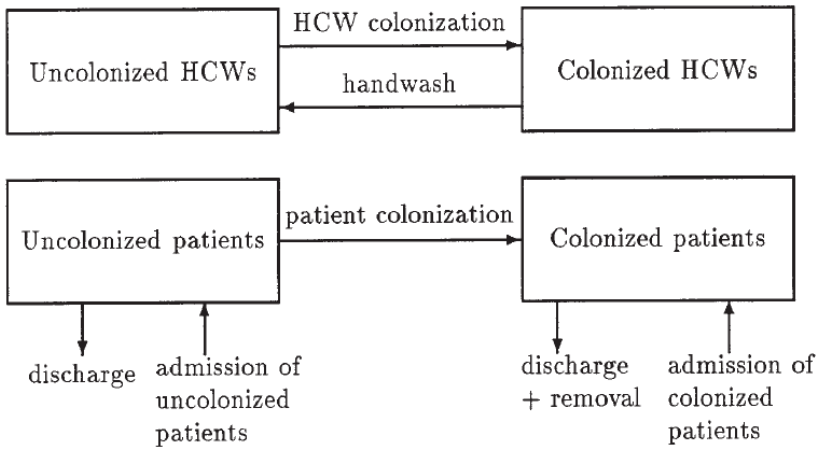

Figure B.1 Flow diagram of the model proposed by Cooper et al. (1999)

Table B.1 Input parameters and default values of the model proposed by Cooper et al. (1999)

Parameter	Meaning	Default value
n	Number of patients	20
n'	Number of health care workers (HCWs)	3
μ	Patient removal rate	0·10/day
μ'	Handwashing rate	14·0/day
γ	Detection rate of colonized patients	0·10/day
σ	Proportion of admissions already colonized	0·01
c	Patient-carer contact rate	5/day
p	Carer-patient transmission probability	0·1
p'	Patient-carer transmission probability	0·1
β	Carer-patient transmission rate ($\beta = cp$)	0·5
β'	Patient-carer transmission rate ($\beta' = cp'$)	0·5

B.2.2 Compare Results

An ABS model is built in Anylogic® to replicate the assumptions of the model. Then the same model experimentations are conducted with the same parameter values (as the previous modelling study) and the results of the ABS model are compared with the results from the original mathematical model.

Scenario 1: Changing Transmissibility

In this scenario, the transmissibility (transmission probability from patient to HCWs and from HCWs to patient per contact) varies from 0 to 0.3. For each level of transmissibility, the ABS model is run 100 times and the mean and the 5th and 95th percentiles are calculated regarding the ward prevalence. Ward prevalence in the study represents the proportion of days in the ward that at least one patient is colonised with MRSA.

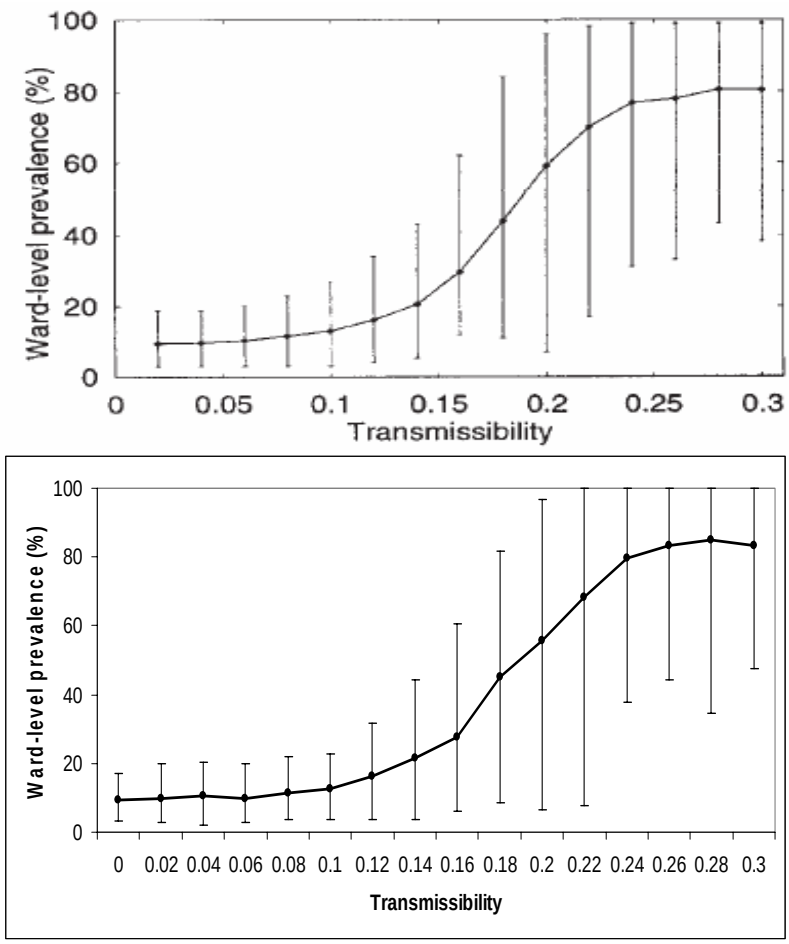

Figure B.2 Comparison between the ABS model and the original model by changing transmissibility (the upper diagram shows the model outputs of the original model (source: Cooper et al. 1999); the lower diagram shows the model outputs of the ABS model)

Figure B.2 compares the model outputs between the ABS model and the original model. The upper diagram, obtained from the original paper, shows the ward-level prevalence from the original model and the lower diagram shows the ward-level prevalence from the ABS model. Under both models, the mean ward prevalence increases from around 10% to around 80% as the transmissibility changes from 0 to 0.3. As in the original model, the ABS model also captures the S-shape increase of the mean ward prevalence, i.e., the mean ward prevalence increases slowly at the beginning, accelerates in the middle, and levels off in the end. Furthermore, the 5th and 95th percentiles of the ward-level prevalence in the ABS model also match that of the original model.

Scenario 2: Changing Probability of Colonisation at Admission

In this scenario, the probability of colonisation at admission varies from 0.01 to 0.1. Each probability is tested on three levels of transmissibility (low 0.07, medium 0.1 and high 0.13). For each combination of the colonisation probability and transmissibility, the ABS model was run 100 times and the mean and the 5th and 95th percentiles (when the transmissibility is set at 0.1) are calculated regarding the ward prevalence.

Figure B.3 compares the model outputs between the ABS model and the original model. The upper diagram, obtained from the original paper, shows the ward-level prevalence of the original model and the lower diagram shows the ward-level prevalence of the ABS model. The two models present similar results. Using both models, the mean ward-level prevalence increases as the probability of colonisation at admission increases from 2% to 10%, regardless of the levels of transmissibility. Both models also demonstrate that, given a certain probability of colonisation at admission, the ward-level prevalence will always be higher with higher level of transmissibility (i.e., the mean ward-level prevalence line representing high level of transmissibility is above the line representing the medium level transmissibility which, in turn, is above the line representing the low level transmissibility). The 5th and 95th percentiles of the mean ward-level prevalence under medium transmissibility of the ABS model also match that of the original model.

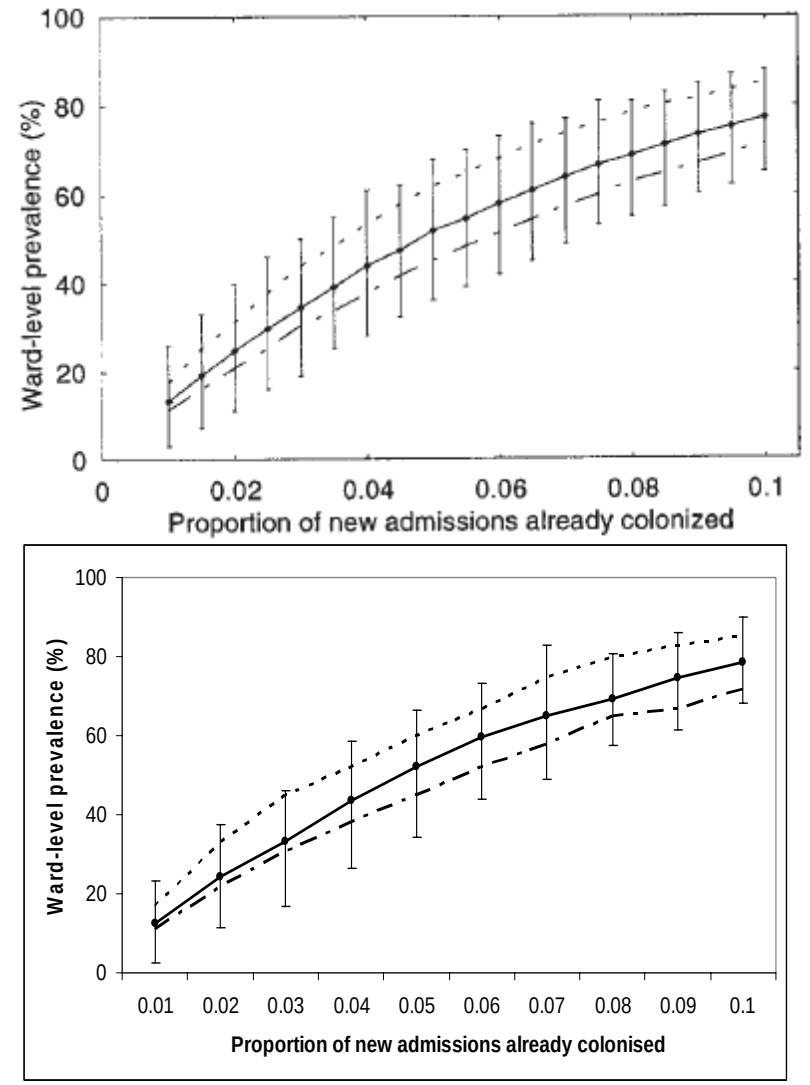

Figure B.3 Comparison between the ABS model and the original model by changing probability of colonisation at admission (the upper diagram shows the model outputs of the original model (source: Cooper et al. 1999); the lower diagram shows the model outputs of the ABS model)

Scenario 3: Changing Detection Rate

In this scenario, the mean time for detection of colonised patients varies from 5 days to 35 days (i.e., detection rate from 0.2 to 0.0286). Each detection rate is tested on three levels of transmissibility (low 0.07, medium 0.1 and high 0.13). For each combination of the colonisation probability and detection rate, the ABS model was run 100 times and the mean and the 5th and 95th percentiles (when the transmissibility is set at 0.1) are calculated regarding the ward prevalence.

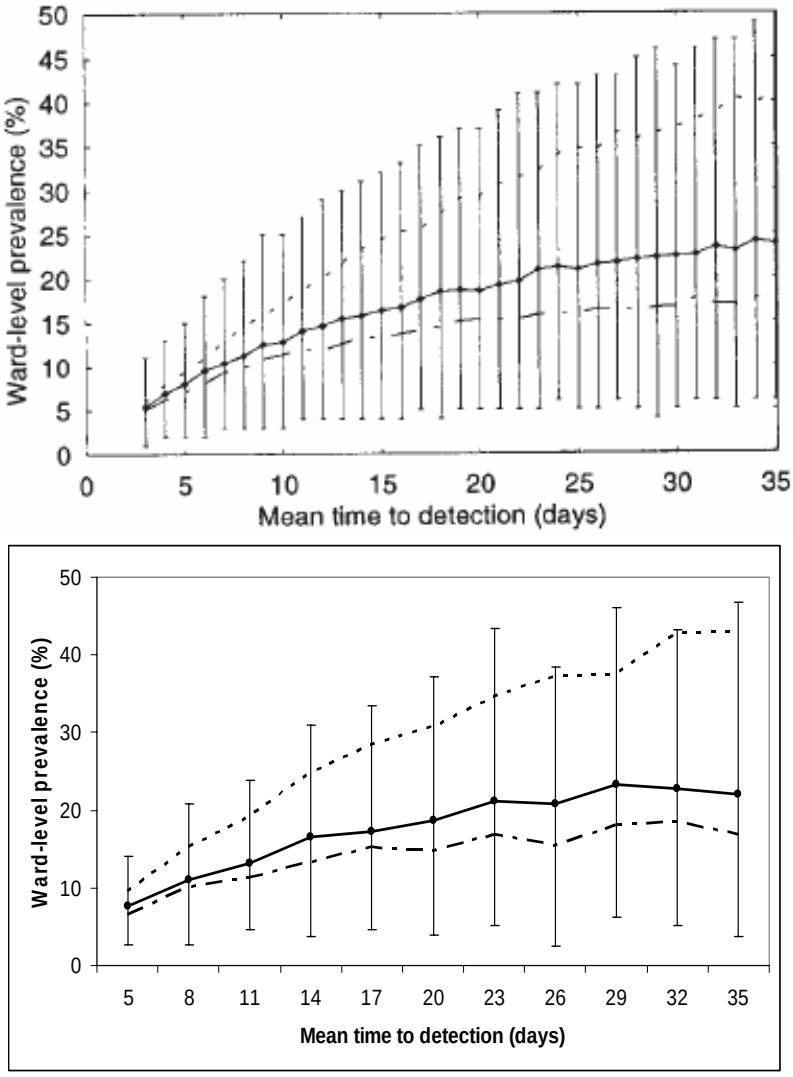

Figure B.4 Comparison between the ABS model and the original model by changing detection rate (the upper diagram shows the model outputs of the original model (source: Cooper et al. 1999); the lower diagram shows the model outputs of the ABS model)

Figure B.4 compares the model outputs between the ABS model and the original model. The upper diagram, obtained from the original paper, shows the ward-level prevalence of the original model and the lower diagram shows the ward-level prevalence of the ABS model. The two models present similar results. Using both models, the mean ward-level prevalence increases in general as the mean time to detection changes from 5 to 35 days, regardless of the levels of transmissibility. Both models also demonstrate that, given a certain mean time to detection, the ward-level prevalence will always be higher with higher level of transmissibility. In both models, when the time to detection reaches 35 days, the mean ward-level prevalence is around 40%, 20% and 15% respectively under high, medium and low level of transmissibility.

The 5th and 95th percentiles of the mean ward-level prevalence under medium transmissibility of the ABS model also match that of the original model.

B.2.3 Conclusions

In all the three scenarios tested, the results of ABS model all closely match that of the compartmental mathematical model proposed by Cooper *et al.* (1999). It demonstrates that ABS can replicate the assumptions and results of the previous MRSA model which considers both HCWs and patients in a single hospital unit. The speed of the ABS model is about 10 seconds for 100 replications with each replication lasting for 365 days on a standard personal desktop computer.

B.3 Test Agent-based Simulation Model on Previous Studies – Part II

B.3.1 Assumptions and Input Parameters

The second model to be tested by ABS model is proposed by Robotham *et al.* (1999). The mathematical compartmental model represented the whole hospital and its community, and divided the patients into eight different compartments. The main assumptions of the model include:

- The model contains the hospital and the community and only patients are explicitly represented in the hospital;
- Transmission only occurs within the hospital and there is no explicit assumptions of how MRSA is transmitted (applying mass action assumption).
- Patients colonised with MRSA can have three statuses: isolated (ISO), detected but not isolated (DNISO) and undetected (UI). As a result, observed hospital prevalence is ISO+DNISO while real hospital prevalence is ISO+DNISO+UI;
- Isolation can totally prevent MRSA transmission, and DNISO and UI patients are equally infectious;
- Discharged patients first enter the community group with higher re-admission rate (C1) and they will move to the second community group with lower re-admission rate (C2) after a delay;
- Positive patients (hospital and community) have equal recovery rate;

- For random screening strategy, after a patient is admitted, the average interval of screening is 1/φ (i.e., the screening rate is φ); and
- For admission screening strategy, a proportion (ω) of patients is screened on admission and there is no further screening carrying out afterwards.

Figure B.5 shows the flow diagram of the model and Table B.2 shows the main input parameters and their default values taken by the model.

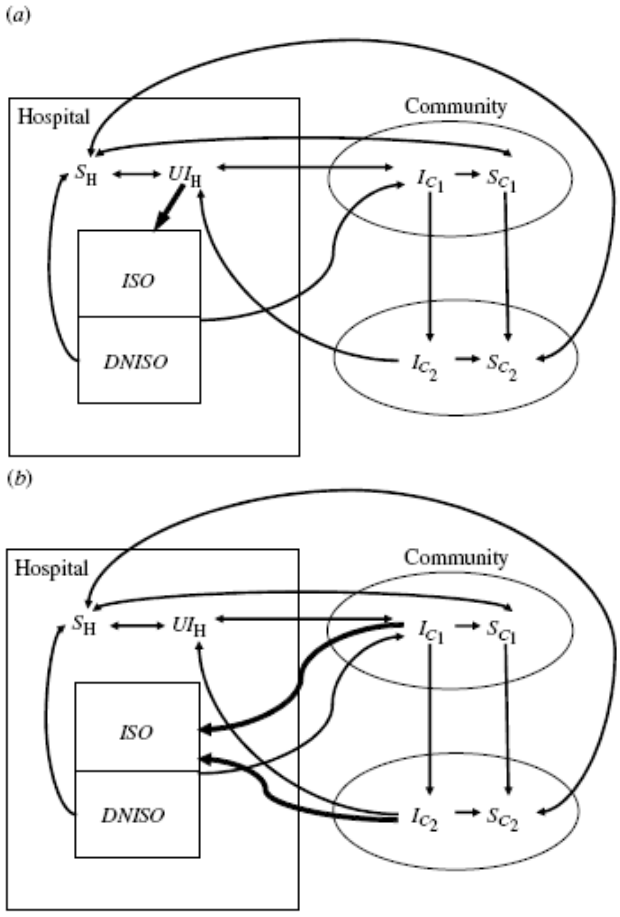

Figure B.5 Flow diagrams of the model proposed by Robotham et al. (2006). (a) Random screening; (b) On-admission screening.

Table B.2 Input parameters and default values of the model proposed by Robotham et al. (2006)

Parameter	Symbol	Value
Transmission coefficient	β	0·1622
Discharge/admission rate (day^{-1})	μ	0·125
Recovery rate (day^{-1})	γ	0·0027
Random screening rate	ϕ	Range: 0·0075–0·125
Admission screening rate	ω	Range: 0·06–1
Readmission rate – community group 1	θ_1	0·0057
Readmission rate – community group 2	θ_2	0·00063
Decay rate from community group 1 to 2	δ	0·03
Community group 1 population size	C_1	Range: $3{\cdot}3263 \times 10^3$ to $3{\cdot}5014 \times 10^3$
Community group 2 population size	C_2	Range: $1{\cdot}584 \times 10^5$ to $1{\cdot}6673 \times 10^5$
Overall community population size	C	Range: $1{\cdot}6172 \times 10^5$ to $1{\cdot}70236 \times 10^5$
Isolation ward capacity	*NISO*	Range: 0–50
Hospital population size	N	1000–*NISO*

B.3.2 Compare Results

The ABS model is built in Anylogic® to replicate the assumptions of the model. Then the same model experimentations are conducted with the same parameter values (as the previous modelling study) and the results of the ABS model are compared with the results of the original mathematical model. Due to the large number of people in the community (i.e., around 170,000 people), only patients in the hospital (i.e., 1000 patients) are represented individually as agent while the different groups of people in the community are represented as global integer variables.

Scenario 1: Real prevalence of hospital and community without isolation facility

In this scenario, the real prevalence of the hospital and community without isolation facility will be compared. The ABS model runs for ten replications and each lasts for 1800 days. Figure A.6 compares the real hospital prevalence between the ABS model and the original mathematical model and Figure A.7 compares the community prevalence between the ABS model and the original model.

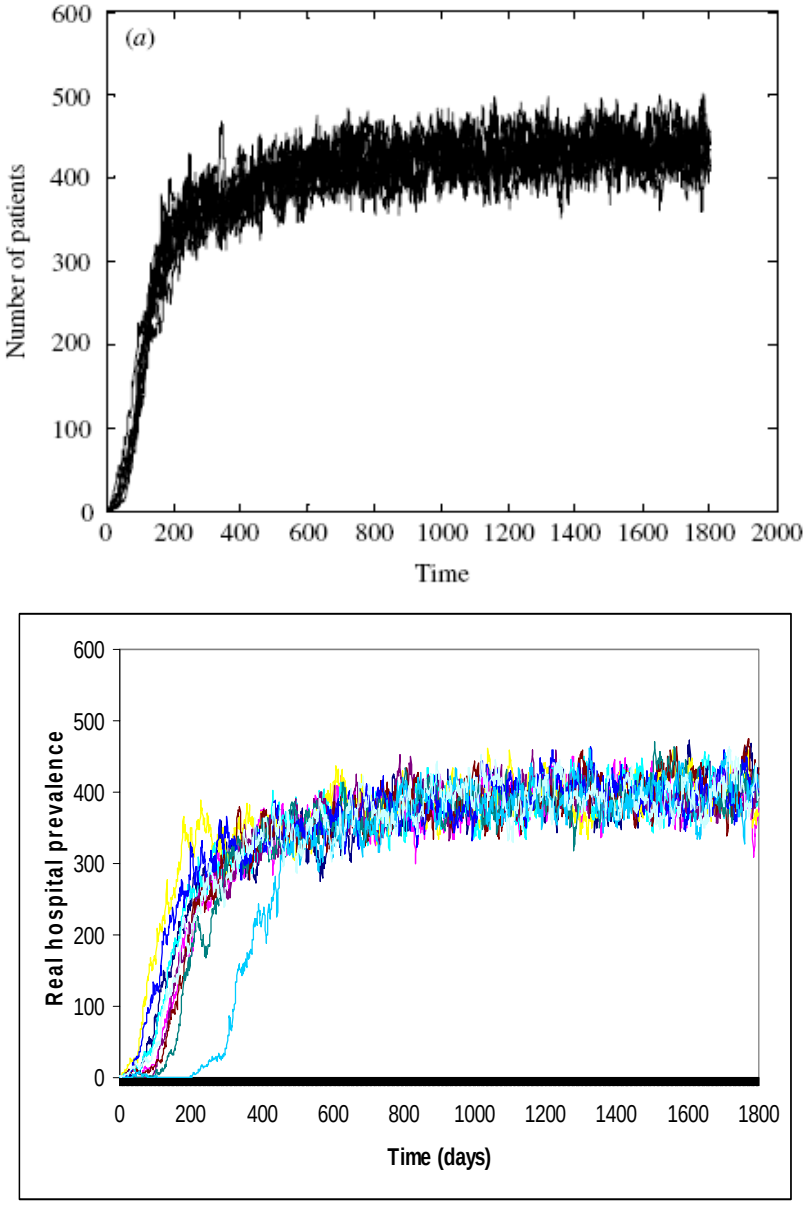

Figure B.6 The comparison of hospital prevalence between the ABS model and the original model (the upper diagram shows the model outputs of the original model (source: Robotham et al. 2006); the lower diagram shows the model outputs of the ABS model)

In Figure B.6, the upper diagram shows the change of real hospital prevalence of the original model from ten replications. The lower diagram shows the change of real hospital prevalence of the ABS model from ten replications. The two models present similar results. Although there are variations among the ten replications, the results from both models demonstrate that the real hospital prevalence increases sharply in the first 200 days from nearly zero to around 300 cases (the capacity of the hospital is 1000). In both models, the real hospital prevalence only increases slightly between 200 days and 800 days and gradually levels off at around 400 cases after 800 days.

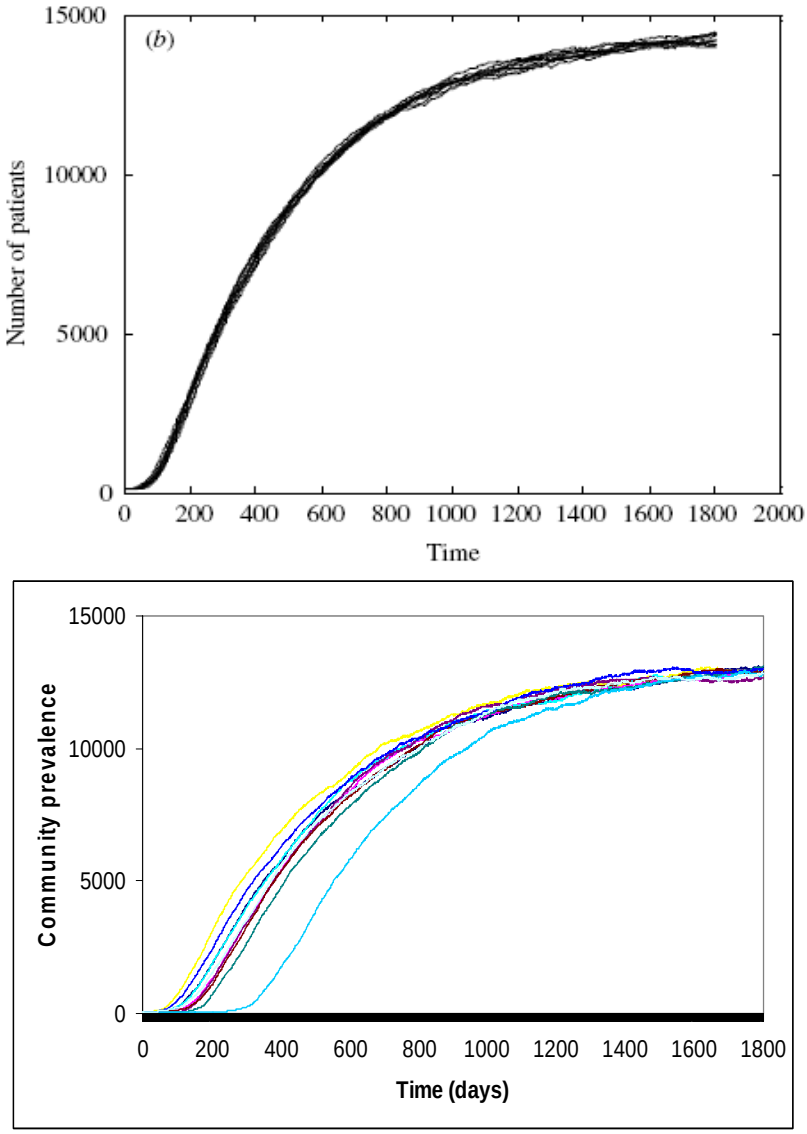

Figure B.7 The comparison of community prevalence between the ABS model and the original model (the upper diagram shows the model outputs of the original model (source: Robotham et al. 2006); the lower diagram shows the model outputs of the ABS model)

In Figure B.7, the upper diagram shows the change of community prevalence of the original model from ten replications. The lower diagram shows the change of community prevalence of the ABS model from ten replications. The two models present similar results. Although there are variations among the ten replications (the variation in the ABS model appears to be bigger than the original model), the increase of the community prevalence is more sharply in the first two years and more smoothly afterwards. After around 1500 days, the community prevalence appears to level off at around 14,000 cases (the size of the community is around 170,000).

Scenario 2: Observed prevalence of hospital

In this scenario, the observed prevalence of the hospital under two screening strategies (random screening and on-admission screening) will be compared. The ABS model runs for ten replications and each lasts for 1800 days. Figure B.8 compares the observed hospital prevalence between the ABS model and the original mathematical model when random screening strategy is adopted. Figure B.9 compares the observed hospital prevalence between the ABS model and the original model when on-admission screening strategy is adopted.

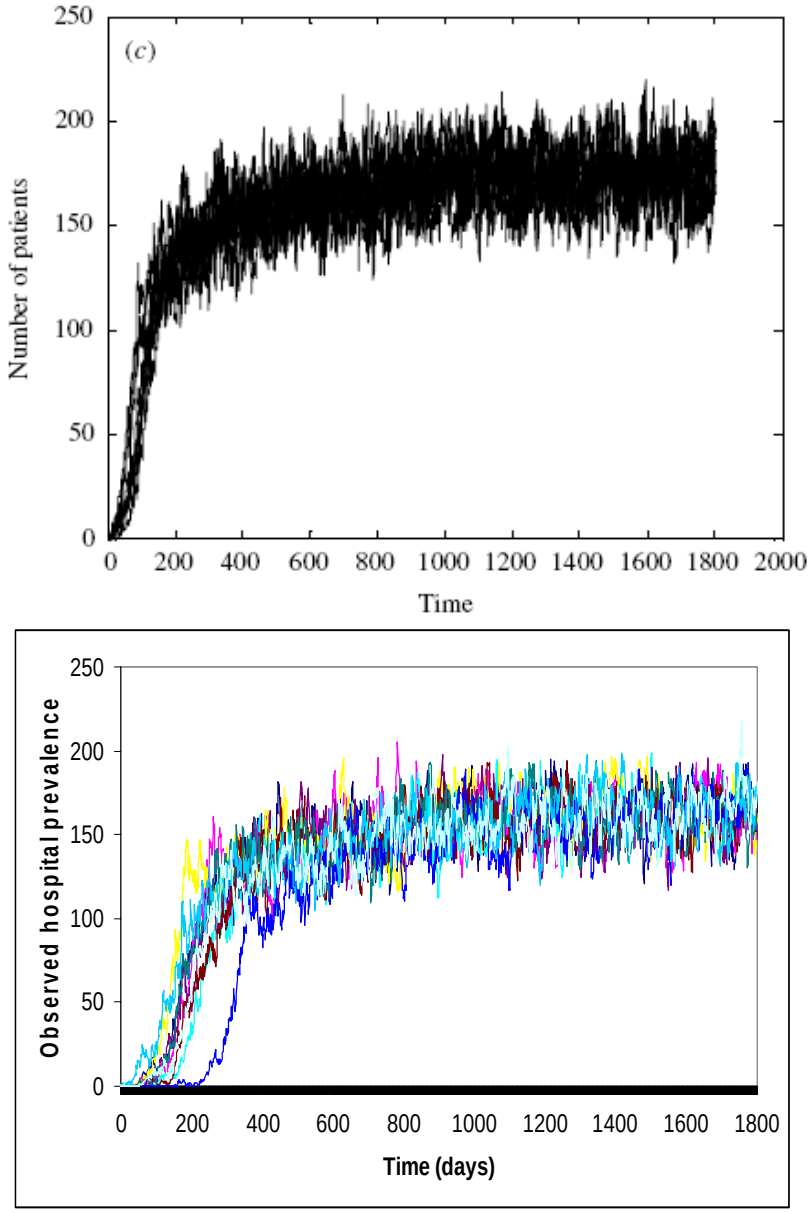

Figure B.8 The comparison of observed hospital prevalence between the ABS model and the original model with random screening strategy (the upper diagram shows the model outputs of the original model (source: Robotham et al. 2006); the lower diagram shows the model outputs of the ABS model)

Assuming the random screening strategy is adopted, the upper diagram in Figure B.8 shows the change of observed hospital prevalence of the original model from ten replications and the lower diagram shows the change of observed hospital prevalence of the ABS model from ten replications. The two models present similar results. Although there are variations among the ten replications, the results from both models demonstrate that the observed hospital prevalence increases sharply at first, more smoothly later and gradually levels off at around 150 cases after about 800 days.

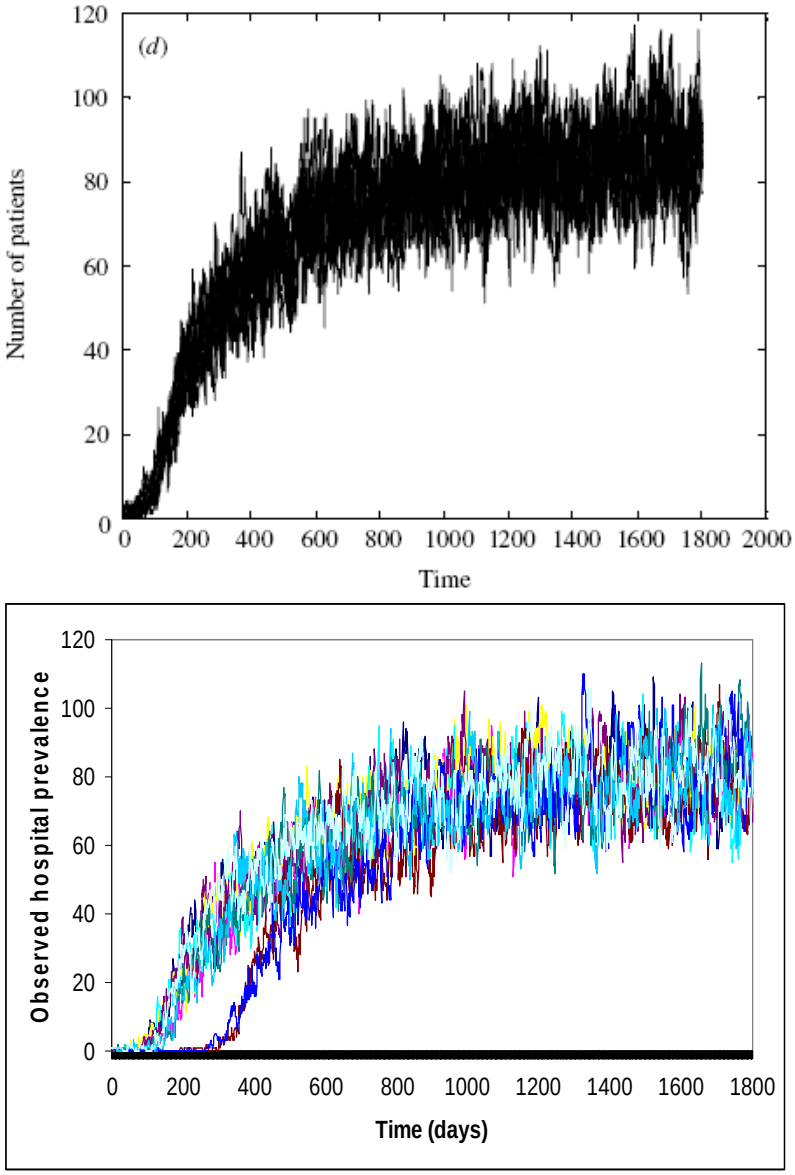

Diagram B.9 The comparison of observed hospital prevalence between the ABS model and the original model with on-admission screening strategy (the upper diagram shows the model outputs of the original model (source: Robotham et al. 2006); the lower diagram shows the model outputs of the ABS model)

Assuming the on-admission screening strategy is adopted, the upper diagram in Figure B.8 shows the change of observed hospital prevalence of the original model from ten replications and the lower diagram shows the change of observed hospital prevalence of the ABS model from the ten replications. The two models present similar results. Although there are variations among ten replications, the results from both models demonstrate that the observed hospital prevalence increases sharply at first, more smoothly later and gradually levels off at around 80 cases after about 1200 days.

Scenario 3: Comparison between random and on-admission screening with isolation

In this scenario, the performance of random and on-admission screening strategy will be compared when an isolation ward is introduced. The comparison will be carried out based on the number of undetected positive patients and the number of patients in the isolation ward. Figures B.10 and B.11 compare the undetected hospital prevalence between the ABS and the original model with random screening strategy and with on-admission screening strategy respectively. Figure B.12 and B.13 compare the number of isolation patients between the ABS and the original model with random screening strategy and with on-admission screening strategy respectively.

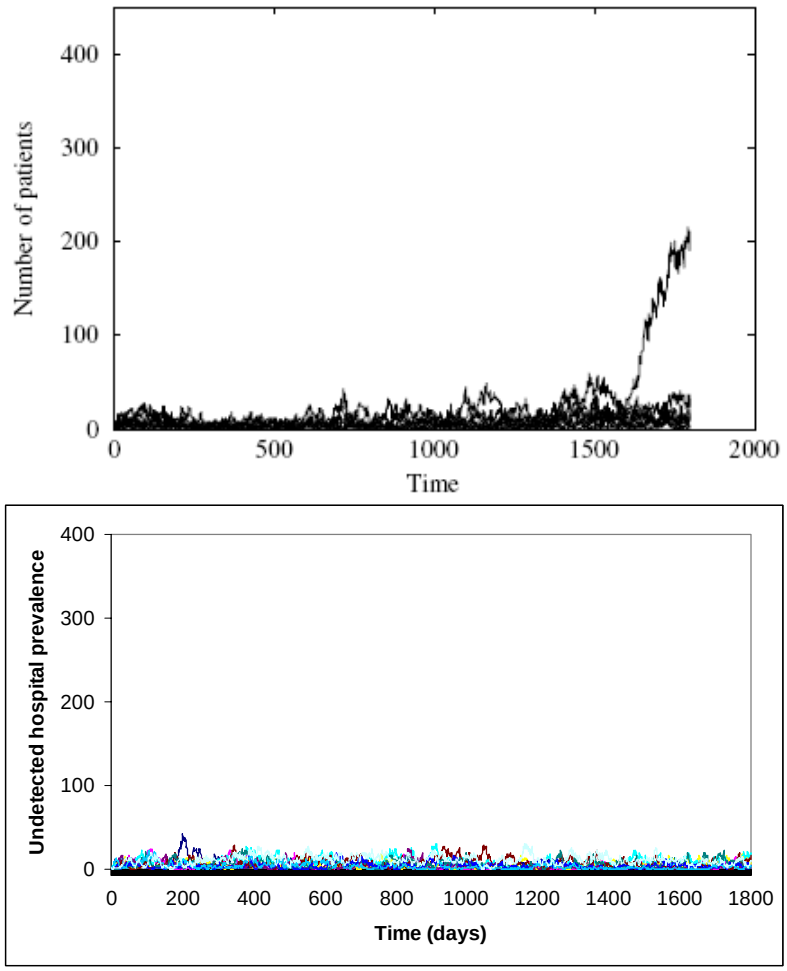

Figure B.10 The comparison of undetected hospital prevalence between the ABS model and the original model with random screening strategy (the upper diagram shows the model outputs of the original model (source: Robotham et al. 2006); the lower diagram shows the model outputs of the ABS model)

Assuming the random screening strategy is adopted, the upper diagram in Figure A.10 shows the change of undetected hospital prevalence of the original model from ten replications and the lower diagram shows the change of undetected hospital prevalence of the ABS model from ten replications. Although there are variations among the ten replications, the results from both models demonstrate that the undetected hospital prevalence remains very low (few cases in a hospital with 1000 beds) through out the whole simulation period.

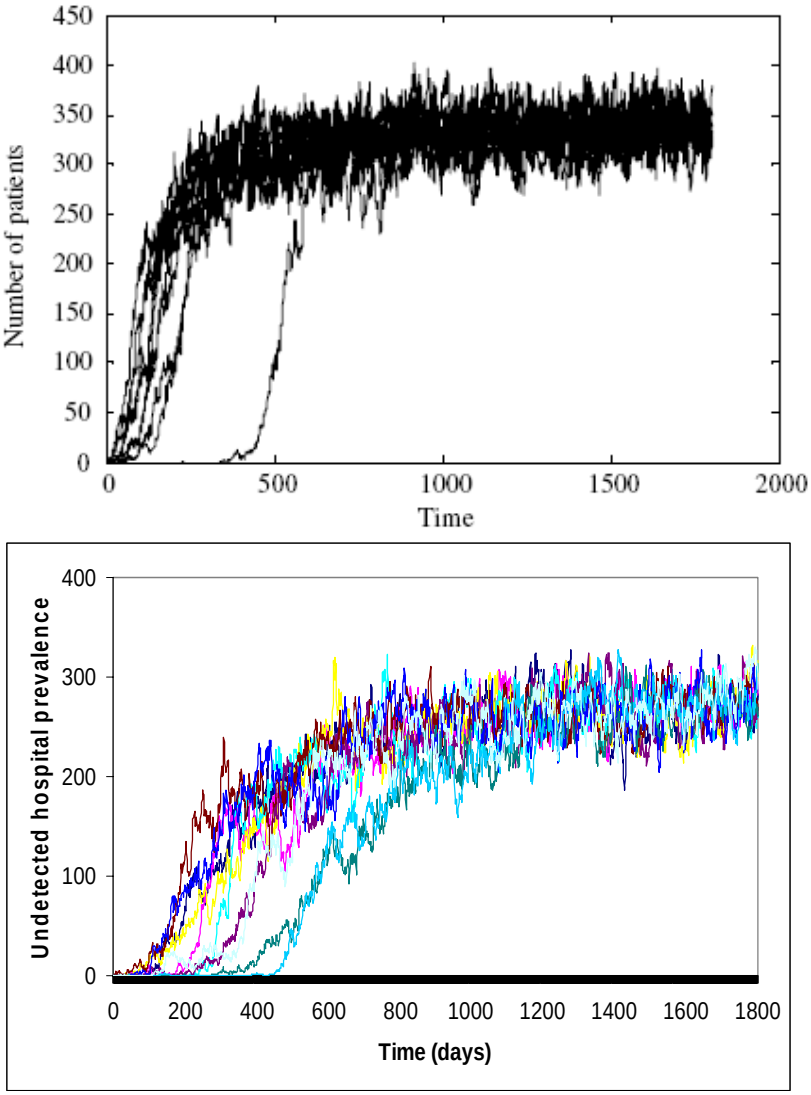

Figure B.11 The comparison of undetected hospital prevalence between the ABS model and the original model with on-admission screening strategy (the upper diagram shows the model outputs of the original model (source: Robotham et al. 2006); the lower diagram shows the model outputs of the ABS model)

Assuming the on-admission screening strategy is adopted, the upper diagram in Diagram A.11 shows the change of undetected hospital prevalence of the original

model from ten replications and the lower diagram shows the change of undetected hospital prevalence of the ABS model from ten replications. Although there are variations among the ten replications, the results from both models are comparable and demonstrate that the undetected hospital prevalence increases sharply at first, more smoothly later and gradually levels off at around 300 cases after about 1000 days.

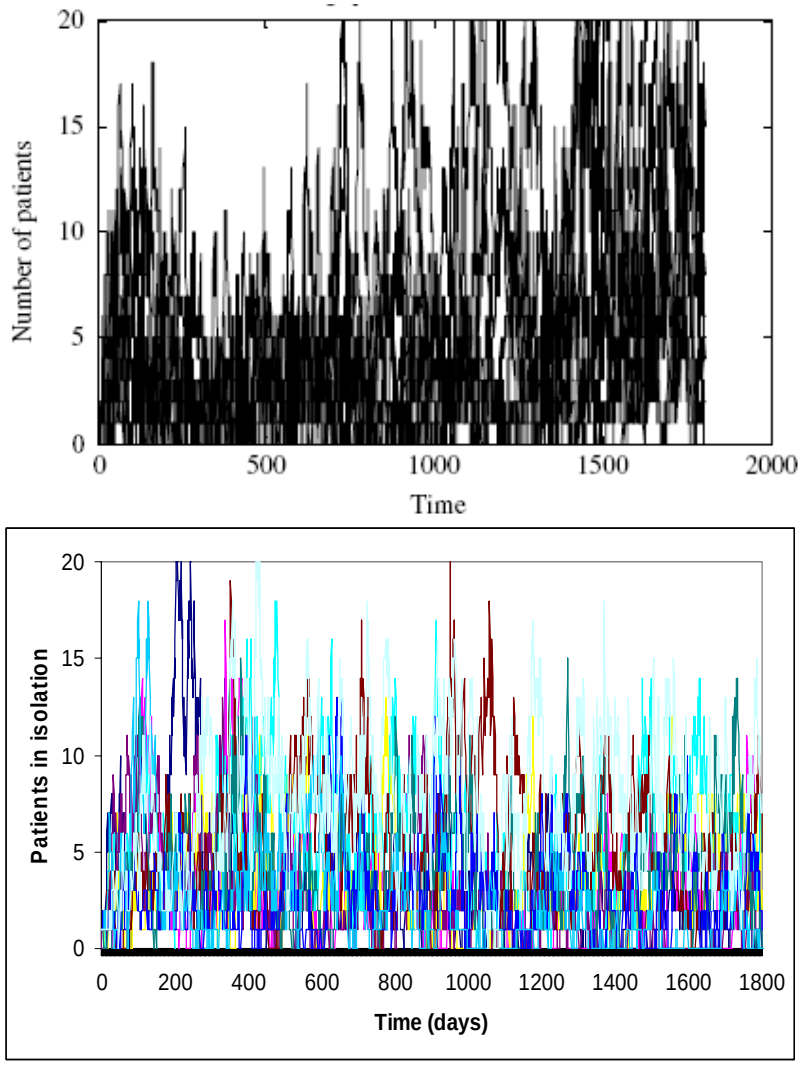

Figure B.12 The comparison of the number of isolation patients between the ABS model and the original model with random screening strategy (the upper diagram shows the model outputs of the original model (source: Robotham et al. 2006); the lower diagram shows the model outputs of the ABS model)

Assuming the random screening strategy is adopted, the upper diagram in Figure A.12 shows the change of isolation patients of the original model from ten replications and the lower diagram shows the change of isolation patients of the ABS model from ten replications. There are huge variations among the ten replications in both models. The

results from both models demonstrate that the number of patients in isolation varies from zero to the maximum capacity of the isolation beds and does not follow any particular pattern through out the whole simulation period. In practice, both models indicate that the isolation facility can meet the demand of the isolation requests in most occasions.

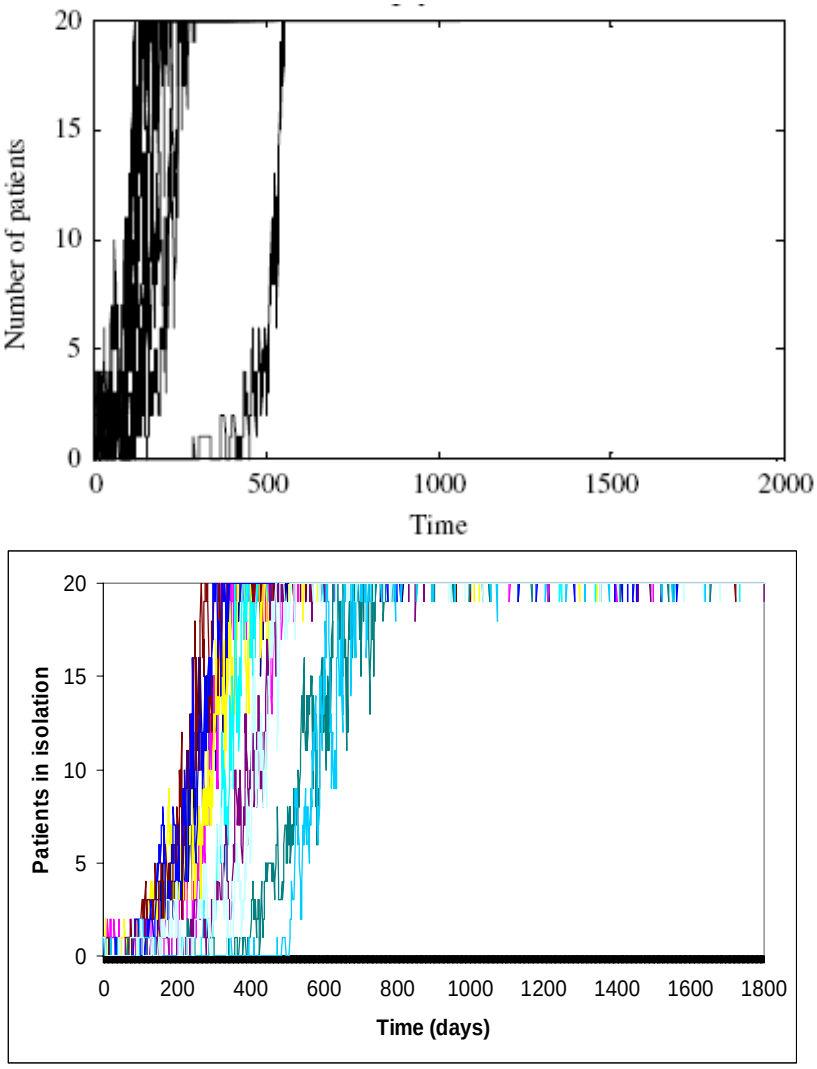

Figure B.13 The comparison of the number of isolation patients between the ABS model and the original model with on-admission screening strategy (the upper diagram shows the model outputs of the original model (source: Robotham et al. 2006); the lower diagram shows the model outputs of the ABS model)

Assuming the on-admission screening strategy is adopted, the upper diagram in Figure B.13 shows the change of isolation patients of the original model from ten replications and the lower diagram shows the change of isolation patients of the ABS model from ten replications. There are variations among the ten replications in both models and the results from both models demonstrate that the number of patients in

isolation increases from zero to the full capacity of the isolation room at first. Then, the isolation room remains almost fully occupied for the rest of the simulation period in both models (which indicates the demand for isolation is constantly higher than the isolation capacity).

B.3.3 Conclusions

In all the scenarios tested, the results of ABS model all closely match that of the mathematical compartmental model proposed by Robotham *et al.* (2006). It demonstrates that ABS can replicate the assumptions and results of the previous MRSA model which considers not only the patients in the hospital but also the feedback relationship between the hospital and the community. The speed of the ABS model is about 30 seconds for ten replications with each lasting for 1800 days on a standard personal desktop computer.

Appendix C

Data Cleaning for the MRSA Case Study

C.1 Data Collection and Storage

According to the research plan, the pre-crossover period was between 1st January 2006 and 31st August 2006 during which Ward A, B, C and D adopted the rapid PCR screening test and Ward E, F and G adopted the conventional culture screening test. The post-crossover period was between 1st September 2006 and 30th April 2007 during which each ward changed the screening test method. Observed data were collected throughout the sixteen-month study period as well as for two months before the pre-crossover period started (to test the data collection procedure and train the data input staff) and for one month after the post-crossover period finished (to collect the follow up data).

Observed data regarding MRSA screening tests, both PCR tests and culture tests, are stored in a single Microsoft Office Excel® file. Each screening test was recorded in the file regarding the identification of the patient (e.g., patient number and patient surname), the ward the patient belongs to, the type of the screening test (e.g., admission screening or repeat screening, and PCR test or culture test) and the time the sample is collected and received by the laboratory.

All the rest of the observed data of the research study were stored in two separate Microsoft Office Access® files. The structures of the two databases are identical. One file is used for storing the data for Ward A, B, C and D during the whole study period and the other file for storing the data for Ward E, F and G during the whole study period. The main tables in the database and the key information recorded in each table are listed below. These main tables and other complementary tables are linked together as a relational database.

- "Patients" table: the key information stored in this table includes patient number, patient name, and the age and sex of the patient;
- "In-Patient" table: the key information stored in this table includes patient number, the MRSA status of the patient (e.g., the date MRSA is identified), follow-up interventions for MRSA positive patient (e.g., date of starting decolonisation treatment, date of starting isolation and reasons for not receiving treatment and not been isolated), potential risk factors of the patient regarding MRSA (e.g., whether the patient has been admitted to ICU, whether the patient has been used invasive devices, whether the patient got operation, and whether the patient got wounds, ulcers and diabetic) and where the patient is admitted from; and
- "WardMovement" table: the key information stored in this table includes the admission and discharge dates of each patient in the hospital ward, the status of discharge (i.e., alive or dead) and the destination of discharge.

C.2 Data Cleaning

Since the screening sample information (stored in an Excel file) and the rest of the observed data (stored in two Access files) are kept in different files, the first task for data cleaning is to link the two sources of information together. The method is to create two new tables in the existing two Access files to represent the screening information (which comes from the Excel screening sample file) and link the new screening sample tables with existing tables. By doing so, the screening sample information of a patient is linked to the rest of the information of the same patient.

Due to the large scale of the research study and the big size of the dataset, there would be inevitably many human errors and inconsistencies among the original data. Once the two Access files include all the observed data (including screening sample information) of the research study, a series of data cleaning tasks were performed to eliminate any input errors and inconsistencies of the data. The original Excel and Access files were available from the hospital in July 2007 and the two final cleaned Access databases (one for Ward A to D and the other for Ward E to F) were finished by October 2007.

Screening Sample Table Cleaning

One of the main tasks of data cleaning is to link each screening sample record with its corresponding ward admission record. In theory, a patient admission may not be associated with any screening sample (e.g., the patient stays too short to have any screening sample been taken) but any screening sample must belong to a particular patient admission and to one of the study wards. If a screening sample can not be associated with any patient admission records, the screening sample records were either corrected by seeking further information or deleted if there was no explanation.

In the original screening sample file, the type of each screening sample is recorded (e.g., admission screening and repeat screening). During data cleaning, the type of each sample is checked by comparing the date the sample is taken with the corresponding ward admission date (from the ward movement table). If the screening sample is taken within two days of admission, the screening sample is labelled as admission screening; otherwise, it is labelled as repeat screening.

In practice, if a patient is screened for MRSA, more than one sample may be taken at the same time (e.g., from the nose and the wound). Under such circumstances, multiple screening sample records will exist for the same patient on the same day. If all the samples give the same result (which happens in most cases), only one screening sample record was retained.

Inconsistencies between Screening Sample Table and In-Patient Table regarding MRSA Status

In some cases the screening sample table shows that the screening sample is positive for a patient while the same patient in the in-patient table is not marked as MRSA positive. There were also cases that a patient in the in-patient table is marked as MRSA positive while the patient does not have any positive screening sample record in the screening sample table. Under such circumstances, careful further review was conducted to determine whether the record in the in-patient table was wrong or a screening sample record was missing in the screening sample table. Then, the records in the relevant tables were modified accordingly.

Ward Movement Table Cleaning

The admission and discharge dates stored in the ward movement table were used to calculate the ward length of stay of each patient. If the length of stay is negative or excessively long (i.e., more than 100 days), further review was conducted. In most cases, the dubious cases were successfully modified according to the clinical records through further review.

Other Data Cleaning Activities

All data that were associated with patients whose discharge date is before 1st January 2006 (the starting date of the pre-crossover period) or whose admission date is after 30th April 2007 (the finishing date of the post-crossover period) were excluded from the final databases.

After performing the data cleaning activities, the final two Access databases are used to estimate the values of various input parameters for the model.

Appendix D

The Relative Risks of ICU Admission and Applying Invasive Device

In epidemiology, relative risk indicates the risk of acquiring an infectious disease in a group of people who were exposed to a risk factor, relative to a group who were not exposed to it (Stewart 2002). In this study, the disease represents the MRSA colonisation and the risk factors include ICU admission and invasive device application (e.g., catheters). A 2x2 table is useful to define and calculate the relative risk (see Table D.1).

Table D.1 A 2x2 table for defining and calculating relative risk

		Acquire the infectious disease?		
		Yes	No	Total
Exposed to the risk factor?	Yes	*a*	*b*	*a* + *b*
	No	*c*	*d*	*c* + *d*
	Total	*a* + *c*	*b* + *d*	*a* + *b* + *c* + *d*

In Table D.1, the total number of patients exposed to the risk factor is (*a* + *b*), among which *a* represents the number of patients who have acquired the infectious disease and *b* represents the number of patients who have not. The total number of patients who have not exposed to the risk fact is *(c + d)*, among which *c* represents the number of patients who have acquired the infectious disease and *d* represents the number of patients who have not. Accordingly, the total number of patients who have acquired the infectious disease, regardless of the risk factor, is *(a + c)*; while *(b + d)* represents the number of patients who have not acquired the disease.

Relative risk is calculated by dividing the probability of acquiring the infectious disease among the patients who are exposed to the risk factor by the probability of

acquiring the disease among the patients who are not exposed to the risk factor. Mathematically, it is calculated as follows:

$$RR = \frac{a/(a+b)}{c/(c+d)}$$

where *RR* represents the relative risk and the rest of the variables are defined in Table D.1.

If the relative risk is bigger than one, there is an increased risk of acquiring the infectious disease if the patient is exposed to the risk factor; while if the relative risk is less than one, there is a decreased risk of acquiring the disease if the patient is exposed to the factor.

In order to calculate the relative risk of ICU admission and invasive device application, three tables are constructed (see Table D.2 to D.4). The values in the tables are counted directly from the observed data from the research study. Since patients who are already colonised with MRSA (i.e., primary cases) are unlikely to acquire MRSA again during the ward stay, the primary case patients are excluded from the estimation of the relative risk. Compared to patients who are neither admitted to ICU nor applied invasive devices, the relative risk of patients who are admitted to ICU but not applied invasive devices is 4.6, the relative risk of patients who are not admitted to ICU but applied invasive devices is 2.33, and the relative risk of patients who are both admitted to ICU and applied invasive devices is 6.23.

Table D.2 Relative risk of patients who are admitted to ICU but not applied invasive devices

		Acquire MRSA?		
		Yes	No	Total
Risk factor	ICU admission but no invasive devices application	17	115	132
	No ICU admission and no invasive devices application	75	2601	2676
	Total	92	2716	2808
Relative risk		4.60		

Table D.3 Relative risk of patients who are not admitted to ICU but applied invasive devices

		Acquire MRSA?		
		Yes	No	Total
Risk factor	Invasive devices application but no ICU admission	551	7891	8442
	No ICU admission and no invasive devices application	75	2601	2676
	Total	626	10492	11118
Relative risk		2.33		

Table D.4 Relative risk of patients who are admitted to ICU and applied invasive devices

		Acquire MRSA?		
		Yes	No	Total
Risk factor	ICU admission and invasive devices application	442	2090	2532
	No ICU admission and no invasive devices application	75	2601	2676
	Total	263	2754	3017
Relative risk		6.23		

Appendix E

Empirical Distributions for the Lengths of Stay

During the model validation, all fourteen scenarios apply empirical distributions to represent patients' actual lengths of stay. For each scenario, two empirical distributions are constructed from the observed data: one for the lengths of stay of non-primary case patients (i.e., patients who are not colonised with MRSA on admission) and the other for the lengths of stay of primary case patients (i.e., patients who have already been colonised with MRSA on admission).

Table E.1 to E.28 show the details of these step-wise empirical distributions. Each of the 14 scenarios has two tables: the first table represents the lengths of stay for non-primary case patients and the second for primary case patients. The second column of each table shows the length of stay that was recorded in the database. The third column shows the observed frequency of that length of stay. The fourth column represents the observed frequency in terms of percentage. The fifth column, based on the fourth column, shows the cumulative percentages. The last column shows how the recorded length of stay is represented in the model. For example, for the third row in Table E.1 (with index 2), it means, among all non-primary case patients during the pre-crossover period for ward A, there are 105 patients whose length of stay is recorded as one day; since the total number of non-primary case patients in the scenario is 1058 (the last row in the table), 105 patients represents 9.924% (105/1058) of all non-primary case patients in the scenario; the cumulative percentage is 11.72% which indicates that 11.72% of non-primary case patients have a length of stay equals or less than one day; and if the recorded length of stay is one day, then it is represented as a uniform distribution between zero and two days in the model.

The reason for using the uniform distribution to represent the short lengths of stay is that the hospital only records the date of admission and discharge without specifying

the exact time of the day (e.g., hours and minutes) the patient is admitted or discharged. So if the recorded length of stay is one day (i.e., the discharge date is one day after the admission date), in extreme cases, the patients may have a length of stay close to zero (e.g., the patient is admitted close midnight and discharged rightly after midnight) or may have a length of stay close to two days (e.g., the patient is admitted rightly after midnight and discharged the following day close to midnight). Since the simulation model assumes continuous time, the actual length of stay of the patient will be sampled from a uniform distribution between zero and two days (the mean length of stay is still one day).

Not all recorded lengths of stay are individually represented in the empirical distribution; some days are aggregated to reduce the number of bins. The rule applied in this study is that if a recorded length of stay has a percentage less than 2%, the length of stay will be grouped with an adjacent longer length of stay so that their combined percentage exceeds 2%. Normally, a long range of length of stay is grouped together at he right tail of the empirical length of stay distribution, since there are only a few scattering cases of extremely long lengths of stay in each scenario (e.g., in pre-crossover period of ward C, the last step of the empirical length of stay ranges from 43 days to 112 days and only contains 16 cases out of a total of 1105 cases). It is assumed that a uniform distribution is not ideal but probably a simple solution as a reasonable rough estimate. This drawback may be mitigated, to some extent, by multiple replications of the simulation run.

Table E.1 Empirical distribution of length of stay for non-primary case patients (pre-crossover period for ward A)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	19	1.796%	1.796%	uniform(0,1)
2	1	105	9.924%	11.720%	uniform(0,2)
3	2	119	11.248%	22.968%	uniform(1,3)
4	3	130	12.287%	35.255%	uniform(2,4)
5	4	100	9.452%	44.707%	uniform(3,5)
6	5	94	8.885%	53.592%	uniform(4,6)
7	6	89	8.412%	62.004%	uniform(5,7)
8	7	75	7.089%	69.093%	uniform(6,8)
9	8	57	5.388%	74.480%	uniform(7,9)
10	9	47	4.442%	78.922%	uniform(8,10)
11	10	50	4.726%	83.648%	uniform(9,11)
12	11	30	2.836%	86.484%	uniform(10,12)
13	(12,13)	32	3.025%	89.509%	uniform(11,14)
14	(14,15)	28	2.647%	92.155%	uniform(13,16)
15	(16,18)	22	2.079%	94.234%	uniform(15,19)
16	(19,22)	22	2.079%	96.314%	uniform(18,23)
17	(23,30)	22	2.079%	98.393%	uniform(22,31)
18	(33,74)	17	1.607%	100.000%	uniform(32,75)
Sum		1058	100%		

LOS: length of stay.

Table E.2 Empirical distribution of length of stay for primary case patients (pre-crossover period of ward A)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	3	5.556%	5.556%	uniform(0,1)
2	1	4	7.407%	12.963%	uniform(0,2)
3	2	6	11.111%	24.074%	uniform(1,3)
4	3	4	7.407%	31.481%	uniform(2,4)
5	4	7	12.963%	44.444%	uniform(3,5)
6	(5,6)	5	9.259%	53.704%	uniform(4,7)
7	7	4	7.407%	61.111%	uniform(6,8)
8	8	3	5.556%	66.667%	uniform(7,9)
9	9	3	5.556%	72.222%	uniform(8,10)
10	12	4	7.407%	79.630%	uniform(11,13)
11	(13,17)	3	5.556%	85.185%	uniform(12,18)
12	(20,21)	3	5.556%	90.741%	uniform(19,22)
13	(24,29)	3	5.556%	96.296%	uniform(23,30)
14	(31,35)	2	3.704%	100.000%	uniform(30,36)
Sum		54	100%		

LOS: length of stay.

Table E.3 Empirical distribution of length of stay for non-primary case patients (post-crossover period for ward A)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	28	2.737%	2.737%	uniform(0,1)
2	1	123	12.023%	14.761%	uniform(0,2)
3	2	123	12.023%	26.784%	uniform(1,3)
4	3	97	9.482%	36.266%	uniform(2,4)
5	4	98	9.580%	45.846%	uniform(3,5)
6	5	88	8.602%	54.448%	uniform(4,6)
7	6	74	7.234%	61.681%	uniform(5,7)
8	7	57	5.572%	67.253%	uniform(6,8)
9	8	69	6.745%	73.998%	uniform(7,9)
10	9	38	3.715%	77.713%	uniform(8,10)
11	10	34	3.324%	81.036%	uniform(9,11)
12	11	21	2.053%	83.089%	uniform(10,12)
13	12	24	2.346%	85.435%	uniform(11,13)
14	13	22	2.151%	87.586%	uniform(12,14)
15	(14,15)	35	3.421%	91.007%	uniform(13,16)
16	(16,18)	24	2.346%	93.353%	uniform(15,19)
17	(19,21)	22	2.151%	95.503%	uniform(18,22)
18	(22,26)	23	2.248%	97.752%	uniform(21,27)
19	(27,53)	21	2.053%	99.804%	uniform(26,54)
20	(62,97)	2	0.196%	100.000%	uniform(61,98)
Sum		1023	100.000%		

LOS: length of stay.

Table E.4 Empirical distribution of length of stay for primary case patients (post-crossover period of ward A)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	1	3	17.647%	17.647%	uniform(0,2)
2	2	1	5.882%	23.529%	uniform(1,3)
3	4	4	23.529%	47.059%	uniform(3,5)
4	7	1	5.882%	52.941%	uniform(6,8)
5	9	2	11.765%	64.706%	uniform(8,10)
6	10	2	11.765%	76.471%	uniform(9,11)
7	12	1	5.882%	82.353%	uniform(11,13)
8	16	1	5.882%	88.235%	uniform(15,17)
9	20	1	5.882%	94.118%	uniform(19,21)
10	26	1	5.882%	100.000%	uniform(25,27)
Sum		17	100%		

LOS: length of stay.

Table E.5 Empirical distribution of length of stay for non-primary case patients (pre-crossover period for ward B)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	117	11.619%	11.619%	uniform(0,1)
2	1	431	42.800%	54.419%	uniform(0,2)
3	2	150	14.896%	69.315%	uniform(1,3)
4	3	76	7.547%	76.862%	uniform(2,4)
5	4	62	6.157%	83.019%	uniform(3,5)
6	5	41	4.071%	87.090%	uniform(4,6)
7	6	26	2.582%	89.672%	uniform(5,7)
8	(7,8)	33	3.277%	92.949%	uniform(6,9)
9	(9,10)	21	2.085%	95.035%	uniform(8,11)
10	(11,15)	21	2.085%	97.120%	uniform(10,16)
11	(17,45)	22	2.185%	99.305%	uniform(16,46)
12	(47,93)	7	0.695%	100.000%	uniform(46,94)
Sum		1007	100%		

LOS: length of stay.

Table E.6 Empirical distribution of length of stay for primary case patients (pre-crossover period of ward B)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	1	8	36.364%	36.364%	uniform(0,2)
2	(2,4)	4	18.182%	54.545%	uniform(1,5)
3	(5,8)	2	9.091%	63.636%	uniform(4,9)
4	9	2	9.091%	72.727%	uniform(8,10)
5	(12,14)	2	9.091%	81.818%	uniform(11,15)
6	(24,31)	2	9.091%	90.909%	uniform(23,32)
7	(43,46)	2	9.091%	100.000%	uniform(42,47)
Sum		22	100.000%		

LOS: length of stay.

Table E.7 Empirical distribution of length of stay for non-primary case patients (post-crossover period for ward B)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	377	18.204%	18.204%	uniform(0,1)
2	1	1201	57.991%	76.195%	uniform(0,2)
3	2	185	8.933%	85.128%	uniform(1,3)
4	3	94	4.539%	89.667%	uniform(2,4)
5	4	50	2.414%	92.081%	uniform(3,5)
6	(5,6)	57	2.752%	94.833%	uniform(4,7)
7	(7,9)	52	2.511%	97.344%	uniform(6,10)
8	(10,29)	42	2.028%	99.372%	uniform(9,30)
9	(30,81)	13	0.628%	100.000%	uniform(29,82)
Sum		2071	100%		

LOS: length of stay.

Table E.8 Empirical distribution of length of stay for primary case patients (post-crossover period of ward B)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	7	28.000%	28.000%	uniform(0,1)
2	1	11	44.000%	72.000%	uniform(0,2)
3	2	1	4.000%	76.000%	uniform(1,3)
4	3	2	8.000%	84.000%	uniform(2,4)
5	4	2	8.000%	92.000%	uniform(3,5)
6	25	2	8.000%	100.000%	uniform(24,26)
Sum		25	100%		

LOS: length of stay.

Table E.9 Empirical distribution of length of stay for non-primary case patients (pre-crossover period for ward C)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	52	4.706%	4.706%	uniform(0,1)
2	1	214	19.367%	24.072%	uniform(0,2)
3	2	196	17.738%	41.810%	uniform(1,3)
4	3	106	9.593%	51.403%	uniform(2,4)
5	4	95	8.597%	60.000%	uniform(3,5)
6	5	64	5.792%	65.792%	uniform(4,6)
7	6	61	5.520%	71.312%	uniform(5,7)
8	7	33	2.986%	74.299%	uniform(6,8)
9	8	34	3.077%	77.376%	uniform(7,9)
10	9	24	2.172%	79.548%	uniform(8,10)
11	10	28	2.534%	82.081%	uniform(9,11)
12	11	24	2.172%	84.253%	uniform(10,12)
13	(12,13)	28	2.534%	86.787%	uniform(11,14)
14	(14,15)	28	2.534%	89.321%	uniform(13,16)
15	(16,19)	27	2.443%	91.764%	uniform(15,20)
16	(20,23)	28	2.534%	94.298%	uniform(19,24)
17	(24,31)	24	2.172%	96.470%	uniform(23,32)
18	(32,43)	23	2.081%	98.551%	uniform(31,44)
19	(44,111)	16	1.448%	99.999%	uniform(43,112)
Sum		1105	100%		

LOS: length of stay.

Table E.10 Empirical distribution of length of stay for primary case patients (pre-crossover period of ward C)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	3	5.556%	5.556%	uniform(0,1)
2	1	4	7.407%	12.963%	uniform(0,2)
3	2	6	11.111%	24.074%	uniform(1,3)
4	3	7	12.963%	37.037%	uniform(2,4)
5	4	5	9.259%	46.296%	uniform(3,5)
6	(5,6)	5	9.259%	55.556%	uniform(4,7)
7	7	5	9.259%	64.815%	uniform(6,8)
8	(9,10)	5	9.259%	74.074%	uniform(8,11)
9	(12,16)	3	5.556%	79.630%	uniform(11,17)
10	(19,28)	5	9.259%	88.889%	uniform(18,29)
11	(31,33)	3	5.556%	94.444%	uniform(30,34)
12	(44,74)	3	5.556%	100.000%	uniform(43,75)
Sum		54	100%		

LOS: length of stay.

Table E.11 Empirical distribution of length of stay for non-primary case patients (post-crossover period for ward C)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	42	3.485%	3.485%	uniform(0,1)
2	1	267	22.158%	25.643%	uniform(0,2)
3	2	200	16.598%	42.241%	uniform(1,3)
4	3	137	11.369%	53.610%	uniform(2,4)
5	4	89	7.386%	60.996%	uniform(4,5)
6	5	75	6.224%	67.220%	uniform(4,6)
7	6	64	5.311%	72.531%	uniform(5,7)
8	7	57	4.730%	77.261%	uniform(6,8)
9	8	42	3.485%	80.747%	uniform(7,9)
10	9	32	2.656%	83.402%	uniform(8,10)
11	(10,11)	42	3.485%	86.887%	uniform(9,12)
12	(12,13)	32	2.656%	89.543%	uniform(11,14)
13	(14,16)	30	2.490%	92.033%	uniform(13,17)
14	(17,20)	29	2.407%	94.440%	uniform(16,21)
15	(21,27)	27	2.241%	96.681%	uniform(20,28)
16	(28,38)	25	2.075%	98.756%	uniform(27,39)
17	(40,115)	15	1.245%	100.001%	uniform(40,116)
Sum		1205	100%		

LOS: length of stay.

Table E.12 Empirical distribution of length of stay for primary case patients (post-crossover period of ward C)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	1	4	17.391%	17.391%	uniform(0,2)
2	2	3	13.043%	30.435%	uniform(1,3)
3	3	3	13.043%	43.826%	uniform(2,4)
4	(4,5)	2	8.696%	52.174%	uniform(3,6)
5	6	3	13.043%	65.217%	uniform(5,7)
6	(7,8)	2	8.696%	73.913%	uniform(6,9)
7	(9,11)	2	8.696%	82.609%	uniform(8,12)
8	(29,31)	2	8.696%	91.304%	uniform(28,32)
9	(35,54)	2	8.696%	100.000%	uniform(34,55)
Sum		23	100%		

LOS: length of stay.

Table E.13 Empirical distribution of length of stay for non-primary case patients (pre-crossover period for ward D)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	8	1.626%	1.626%	uniform(0,1)
2	1	46	9.350%	10.976%	uniform(0,2)
3	2	62	12.602%	23.577%	uniform(1,3)
4	3	51	10.366%	33.943%	uniform(2,4)
5	4	42	8.537%	42.480%	uniform(3,5)
6	5	34	6.911%	49.390%	uniform(4,6)
7	6	36	7.317%	56.707%	uniform(5,7)
8	7	16	3.252%	59.959%	uniform(6,8)
9	8	23	4.675%	64.634%	uniform(7,9)
10	9	13	2.642%	67.276%	uniform(8,10)
11	10	13	2.642%	69.919%	uniform(9,11)
12	11	14	2.846%	72.764%	uniform(10,12)
13	12	10	2.033%	74.797%	uniform(11,13)
14	13	14	2.846%	77.642%	uniform(12,14)
15	(14,15)	14	2.846%	80.488%	uniform(13,16)
16	(16,17)	17	3.455%	83.943%	uniform(15,18)
17	(18,19)	11	2.236%	86.179%	uniform(17,20)
18	(20,22)	12	2.439%	88.618%	uniform(19,23)
19	(23,28)	11	2.236%	90.854%	uniform(22,29)
20	(29,34)	11	2.236%	93.090%	uniform(28,35)
21	(35,38)	10	2.033%	95.123%	uniform(34,39)
22	(39,50)	10	2.033%	97.156%	uniform(38,51)
23	(53,76)	10	2.033%	99.189%	uniform(52,77)
24	(83,114)	4	0.813%	100.002%	uniform(82,115)
Sum		492	100%		

LOS: length of stay.

Table E.14 Empirical distribution of length of stay for primary case patients (pre-crossover period of ward D)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	1	1	7.143%	7.143%	uniform(0,2)
2	2	1	7.143%	14.286%	uniform(1,3)
3	3	2	14.286%	28.571%	uniform(2,4)
4	4	1	7.143%	35.714%	uniform(3,5)
5	6	1	7.143%	42.857%	uniform(5,7)
6	9	1	7.143%	50.000%	uniform(8,10)
7	18	1	7.143%	57.143%	uniform(17,19)
8	22	1	7.143%	64.286%	uniform(21,23)
9	23	1	7.143%	71.429%	uniform(22,24)
10	31	1	7.143%	78.571%	uniform(30,32)
11	44	1	7.143%	85.714%	uniform(43,45)
12	56	1	7.143%	92.857%	uniform(55,57)
13	84	1	7.143%	100.000%	uniform(83,85)
Sum		14	100%		

LOS: length of stay.

Table E.15 Empirical distribution of length of stay for non-primary case patients (post-crossover period for ward D)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	15	2.517%	2.517%	uniform(0,1)
2	1	90	15.101%	17.617%	uniform(0,2)
3	2	93	15.604%	33.221%	uniform(1,3)
4	3	46	7.718%	40.940%	uniform(2,4)
5	4	40	6.711%	47.651%	uniform(3,5)
6	5	41	6.879%	54.530%	uniform(4,6)
7	6	40	6.711%	61.242%	uniform(5,7)
8	7	15	2.517%	63.758%	uniform(6,8)
9	8	23	3.859%	67.617%	uniform(7,9)
10	9	17	2.852%	70.470%	uniform(8,10)
11	10	20	3.356%	73.826%	uniform(9,11)
12	11	17	2.852%	76.678%	uniform(10,12)
13	12	18	3.020%	79.698%	uniform(11,13)
14	(13,14)	17	2.852%	82.550%	uniform(12,15)
15	(15,16)	21	3.523%	86.073%	uniform(14,17)
16	(17,19)	13	2.181%	88.254%	uniform(16,20)
17	(20,23)	12	2.013%	90.267%	uniform(19,24)
18	(24,27)	13	2.181%	92.448%	uniform(23,28)
19	(28,31)	13	2.181%	94.629%	uniform(27,32)
20	(32,41)	12	2.013%	96.642%	uniform(31,42)
21	(42,58)	12	2.013%	98.655%	uniform(41,59)
22	(67,158)	8	1.342%	99.997%	uniform(66,159)
Sum		596	100%		

LOS: length of stay.

Table E.16 Empirical distribution of length of stay for primary case patients (post-crossover period of ward D)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	1	9.091%	9.091%	uniform(0,1)
2	1	4	36.364%	45.455%	uniform(0,2)
3	2	1	9.091%	54.545%	uniform(1,3)
4	17	1	9.091%	63.636%	uniform(16,18)
5	32	1	9.091%	72.727%	uniform(31,33)
6	35	1	9.091%	81.818%	uniform(34,36)
7	46	1	9.091%	90.909%	uniform(45,47)
8	66	1	9.091%	100.000%	uniform(65,67)
Sum		11	100%		

LOS: length of stay.

Table E.17 Empirical distribution of length of stay for non-primary case patients (pre-crossover period for ward E)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	26	3.818%	3.818%	uniform(0,1)
2	1	99	14.537%	18.355%	uniform(0,2)
3	2	119	17.474%	35.830%	uniform(1,3)
4	3	79	11.601%	47.430%	uniform(2,4)
5	4	75	11.013%	58.443%	uniform(3,5)
6	5	59	8.664%	67.107%	uniform(4,6)
7	6	54	7.930%	75.037%	uniform(5,7)
8	7	26	3.818%	78.855%	uniform(6,8)
9	8	20	2.937%	81.791%	uniform(7,9)
10	9	16	2.349%	84.141%	uniform(8,10)
11	(10,12)	18	2.643%	86.784%	uniform(9,13)
12	(13,14)	14	2.056%	88.840%	uniform(12,15)
13	(15,17)	16	2.349%	91.189%	uniform(14,18)
14	(18,21)	15	2.203%	93.392%	uniform(17,22)
15	(22,27)	14	2.056%	95.448%	uniform(21,28)
16	(30,36)	14	2.056%	97.504%	uniform(29,37)
17	(37,86)	14	2.056%	99.560%	uniform(36,87)
18	(87,145)	3	0.441%	100.001%	uniform(86,146)
Sum		681	100%		

LOS: length of stay.

Table E.18 Empirical distribution of length of stay for primary case patients (pre-crossover period of ward E)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	1	2	10.526%	10.526%	uniform(0,2)
2	2	1	5.263%	15.789%	uniform(1,3)
3	3	1	5.263%	21.053%	uniform(2,4)
4	4	1	5.263%	26.316%	uniform(3,5)
5	5	1	5.263%	31.579%	uniform(4,6)
6	6	1	5.263%	36.842%	uniform(5,7)
7	7	2	10.526%	47.368%	uniform(6,8)
8	9	1	5.263%	52.632%	uniform(8,10)
9	11	2	10.526%	63.158%	uniform(10,12)
10	12	2	10.526%	73.684%	uniform(11,13)
11	13	1	5.263%	78.947%	uniform(12,14)
12	14	1	5.263%	84.211%	uniform(13,15)
13	21	1	5.263%	89.474%	uniform(20,22)
14	43	1	5.263%	94.737%	uniform(42,44)
15	121	1	5.263%	100.000%	uniform(120,122)
Sum		19	100%		

LOS: length of stay.

Table E.19 Empirical distribution of length of stay for non-primary case patients (post-crossover period for ward E)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	22	2.899%	2.899%	uniform(0,1)
2	1	162	21.344%	24.242%	uniform(0,2)
3	2	117	15.415%	39.657%	uniform(1,3)
4	3	80	10.540%	50.198%	uniform(2,4)
5	4	69	9.091%	59.289%	uniform(3,5)
6	5	60	7.905%	67.194%	uniform(4,6)
7	6	55	7.246%	74.440%	uniform(5,7)
8	7	37	4.875%	79.315%	uniform(6,8)
9	8	31	4.084%	83.399%	uniform(7,9)
10	9	24	3.162%	86.561%	uniform(8,10)
11	(10,11)	22	2.899%	89.460%	uniform(9,12)
12	(12,13)	16	2.108%	91.568%	uniform(11,14)
13	(14,16)	18	2.372%	93.940%	uniform(13,17)
14	(17,21)	17	2.240%	96.180%	uniform(16,22)
15	(23,33)	18	2.372%	98.552%	uniform(22,34)
16	(34,81)	11	1.449%	100.001%	uniform(33,82)
Sum		759	100%		

LOS: length of stay.

Table E.20 Empirical distribution of length of stay for primary case patients (post-crossover period of ward E)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	1	6	15.385%	15.385%	uniform(0,2)
2	2	8	20.513%	35.897%	uniform(1,3)
3	3	2	5.128%	41.026%	uniform(2,4)
4	4	4	10.256%	51.282%	uniform(3,5)
5	5	3	7.692%	58.974%	uniform(4,6)
6	6	2	5.128%	64.103%	uniform(5,7)
7	7	2	5.128%	69.231%	uniform(6,8)
8	9	2	5.128%	74.359%	uniform(8,10)
9	(10,11)	3	7.692%	82.051%	uniform(9,12)
10	13	3	7.692%	89.744%	uniform(12,14)
11	(15,18)	2	5.128%	94.872%	uniform(14,19)
12	(39,51)	2	5.128%	100.000%	uniform(38,52)
Sum		39	100%		

LOS: length of stay.

Table E.21 Empirical distribution of length of stay for non-primary case patients (pre-crossover period for ward F)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	50	4.062%	4.062%	uniform(0,1)
2	1	228	18.522%	22.583%	uniform(0,2)
3	2	197	16.003%	38.587%	uniform(1,3)
4	3	144	11.698%	50.284%	uniform(2,4)
5	4	95	7.717%	58.002%	uniform(3,5)
6	5	75	6.093%	64.094%	uniform(4,6)
7	6	61	4.955%	69.050%	uniform(5,7)
8	7	52	4.224%	73.274%	uniform(6,8)
9	8	62	5.037%	78.310%	uniform(7,9)
10	9	40	3.249%	81.560%	uniform(8,10)
11	10	27	2.193%	83.753%	uniform(9,11)
12	(11,12)	33	2.681%	86.434%	uniform(10,13)
13	(13,14)	31	2.518%	88.952%	uniform(12,15)
14	(15,17)	33	2.681%	91.633%	uniform(14,18)
15	(18,21)	29	2.356%	93.989%	uniform(17,22)
16	(22,29)	29	2.356%	96.345%	uniform(21,30)
17	(30,36)	25	2.031%	98.376%	uniform(29.37)
18	(37,167)	20	1.625%	100.001%	uniform(36,168)
Sum		1231	100%		

LOS: length of stay.

Table E.22 Empirical distribution of length of stay for primary case patients (pre-crossover period of ward F)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	1	3.030%	3.030%	uniform(0,1)
2	1	5	15.152%	18.182%	uniform(0,2)
3	2	6	18.182%	36.364%	uniform(1,3)
4	(3,4)	4	12.121%	48.485%	uniform(2,5)
5	(5,6)	3	9.091%	57.576%	uniform(4,7)
6	(7,8)	3	9.091%	66.667%	uniform(6,9)
7	10	3	9.091%	75.758%	uniform(9,11)
8	(11,12)	2	6.061%	81.818%	uniform(10,13)
9	(13,14)	2	6.061%	87.879%	uniform(12,15)
10	(16,21)	2	6.061%	93.939%	uniform(15,22)
11	(38,55)	2	6.061%	100.000%	uniform(37,56)
Sum		33	100%		

LOS: length of stay.

Table E.23 Empirical distribution of length of stay for non-primary case patients (post-crossover period for ward F)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	46	3.830%	3.830%	uniform(0,1)
2	1	211	17.569%	21.399%	uniform(0,2)
3	2	190	15.820%	37.219%	uniform(1,3)
4	3	109	9.076%	46.295%	uniform(2,4)
5	4	102	8.493%	54.788%	uniform(3,5)
6	5	84	6.994%	61.782%	uniform(4,6)
7	6	72	5.995%	67.777%	uniform(5,7)
8	7	54	4.496%	72.273%	uniform(6,8)
9	8	58	4.829%	77.102%	uniform(7,9)
10	9	39	3.247%	80.350%	uniform(8,10)
11	10	33	2.748%	83.097%	uniform(9,11)
12	11	31	2.581%	85.679%	uniform(10,12)
13	(12,13)	46	3.830%	89.509%	uniform(11,14)
14	(14,15)	34	2.831%	92.340%	uniform(13,16)
15	(16,18)	32	2.664%	95.004%	uniform(15,19)
16	(19,23)	26	2.165%	97.169%	uniform(18,24)
17	(24,46)	25	2.082%	99.251%	uniform(23,47)
18	(51,111)	9	0.749%	100.000%	uniform(50,112)
Sum		1201	100%		

LOS: length of stay.

Table E.24 Empirical distribution of length of stay for primary case patients (post-crossover period of ward F)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	1	2.222%	2.222%	uniform(0,1)
2	1	8	17.778%	20.000%	uniform(0,2)
3	2	3	6.667%	26.667%	uniform(1,3)
4	3	10	22.222%	48.889%	uniform(2,4)
5	4	7	15.556%	64.444%	uniform(3,5)
6	(5,6)	6	13.333%	77.778%	uniform(4,7)
7	(7,8)	3	6.667%	84.444%	uniform(6,9)
8	9	4	8.889%	93.333%	uniform(8,10)
9	(11,33)	3	6.667%	100.000%	uniform(10,34)
Sum		45	100%		

LOS: length of stay.

Table E.25 Empirical distribution of length of stay for non-primary case patients (pre-crossover period for ward G)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	12	2.614%	2.614%	uniform(0,1)
2	1	45	9.804%	12.418%	uniform(0,2)
3	2	51	11.111%	23.529%	uniform(1,3)
4	3	40	8.715%	32.244%	uniform(2,4)
5	4	27	5.882%	38.126%	uniform(3,5)
6	5	27	5.882%	44.009%	uniform(4,6)
7	6	22	4.793%	48.802%	uniform(5,7)
8	7	18	3.922%	52.723%	uniform(6,8)
9	8	12	2.614%	55.338%	uniform(7,9)
10	9	18	3.922%	59.259%	uniform(8,10)
11	10	15	3.268%	62.527%	uniform(9,11)
12	11	11	2.397%	64.924%	uniform(10,12)
13	12	16	3.486%	68.410%	uniform(11,13)
14	(13,14)	23	5.011%	73.421%	uniform(12,15)
15	15	11	2.397%	75.818%	uniform(14,16)
16	(16,17)	10	2.179%	77.997%	uniform(15,18)
17	(18,19)	12	2.614%	80.611%	uniform(17,20)
18	20	11	2.397%	83.008%	uniform(19,21)
19	(21,24)	12	2.614%	85.622%	uniform(20,25)
20	(25,28)	11	2.397%	88.019%	uniform(24,29)
21	(29,34)	12	2.614%	90.633%	uniform(28,35)
22	(35,37)	11	2.397%	93.030%	uniform(34,38)
23	(38,44)	10	2.179%	95.209%	uniform(37,45)
24	(45,50)	10	2.179%	97.388%	uniform(44,51)
25	(53,97)	10	2.179%	99.567%	uniform(52,98)
26	(101,102)	2	0.436%	100.003%	uniform(100,103)
Sum		459	100%		

LOS: length of stay.

Table E.26 Empirical distribution of length of stay for primary case patients (pre-crossover period of ward G)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	1	5.556%	5.556%	uniform(0,1)
2	2	2	11.111%	16.667%	uniform(1,3)
3	3	1	5.556%	22.222%	uniform(2,4)
4	4	2	11.111%	33.333%	uniform(3,5)
5	5	3	16.667%	50.000%	uniform(4,6)
6	7	1	5.556%	55.556%	uniform(6,8)
7	10	2	11.111%	66.667%	uniform(9,11)
8	16	1	5.556%	72.222%	uniform(15,17)
9	17	1	5.556%	77.778%	uniform(16,18)
10	21	1	5.556%	83.333%	uniform(20,22)
11	53	1	5.556%	88.889%	uniform(52,54)
12	59	1	5.556%	94.444%	uniform(58,60)
13	73	1	5.556%	100.000%	uniform(72,74)
Sum		18	100%		

LOS: length of stay.

Table E.27 Empirical distribution of length of stay for non-primary case patients (post-crossover period for ward G)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	0	11	2.079%	2.079%	uniform(0,1)
2	1	74	13.989%	16.068%	uniform(0,2)
3	2	68	12.854%	28.922%	uniform(1,3)
4	3	50	9.452%	38.374%	uniform(2,4)
5	4	43	8.129%	46.503%	uniform(3,5)
6	5	32	6.049%	52.552%	uniform(4,6)
7	6	23	4.348%	56.900%	uniform(5,7)
8	7	16	3.025%	59.924%	uniform(6,8)
9	8	23	4.348%	64.272%	uniform(7,9)
10	9	17	3.214%	67.486%	uniform(8,10)
11	10	17	3.214%	70.699%	uniform(9,11)
12	11	16	3.025%	73.724%	uniform(10,12)
13	(12,13)	18	3.403%	77.127%	uniform(11,14)
14	14	14	2.647%	79.774%	uniform(13,15)
15	15	16	3.025%	82.799%	uniform(14,16)
16	(16,18)	11	2.079%	84.878%	uniform(15,19)
17	(19,21)	14	2.647%	87.525%	uniform(18,22)
18	(22,25)	12	2.268%	89.793%	uniform(21,26)
19	(26,30)	12	2.268%	92.061%	uniform(25,31)
20	(31,35)	12	2.268%	94.329%	uniform(30,36)
21	(36,45)	11	2.079%	96.408%	uniform(35,46)
22	(46,53)	11	2.079%	98.487%	uniform(45,54)
23	(55,115)	8	1.512%	99.999%	uniform(54,116)
Sum		529	100%		

LOS: length of stay.

Table E.28 Empirical distribution of length of stay for primary case patients (post-crossover period of ward G)

Index	Recorded LOS (days)	Frequency	Percentage (%)	Cumulative Percentage (%)	Model LOS (days)
1	1	1	7.143%	7.143%	uniform(0,2)
2	2	2	14.286%	21.429%	uniform(1,3)
3	4	1	7.143%	28.571%	uniform(3,5)
4	5	1	7.143%	35.714%	uniform(4,6)
5	8	1	7.143%	42.857%	uniform(7,9)
6	9	1	7.143%	50.000%	uniform(8,10)
7	11	1	7.143%	57.143%	uniform(10,12)
8	19	1	7.143%	64.286%	uniform(18,20)
9	28	1	7.143%	71.429%	uniform(27,29)
10	43	1	7.143%	78.571%	uniform(42,44)
11	45	1	7.143%	85.714%	uniform(44,46)
12	68	1	7.143%	92.857%	uniform(67,69)
13	104	1	7.143%	100.000%	uniform(103,105)
Sum		14	100%		

LOS: length of stay.

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