# The epidemiology, transmission dynamics and control of healthcare-associated infections

Julie Robotham BSc

Submitted for the degree of Doctor of Philosophy

University of Warwick

Department of Biological Sciences

May 2007

# Contents

# List of Figures

# List of Tables

# Acknowledgements

Firstly, I would like to thank my supervisor Graham Medley whose influence goes back to the beginning of my undergraduate career. It was the very first lectures in population dynamics and infectious diseases that sparked my interest in epidemiology and eventually lead to this PhD. As well as for inspiring me, I would like to thank him for his continued guidance and support, but most of all for having confidence in me throughout.

Thanks also to all those at the University Hospitals of Leicester NHS Trust whose involvement has, most importantly, brought home that HCAI are a very real problem, happening to real people, on a day to day basis; it is this, above all else, that has provided my motivation throughout the project. Specifically, I would like to thank Dr. David Jenkins (Consultant Clinical Microbiologist and Lead Infection Control Officer) whose endless enthusiasm and incredible drive could not fail to influence me. Throughout the project he has provided me with inspiration, advice and many interesting and helpful discussions; I am sincerely grateful for all his help. I would also like to add in here a quick thank you to David's secretary Audrey Wright who has, on countless occasions, helped me get in contact with a very busy man!

Also I would like to thank the infection control nurses at UHL who have not only provided me with helpful discussions but also great company at numerous meetings and conferences! I would also like to thank Andrew Folwell (Senior Medical Laboratory Scientific Officer), for generously giving me his time to show me the culturing processes and techniques performed at the hospital. Also a very big thank you goes to Simon Sutherland, the Trust's Senior Pathway Information

Analyst, for providing and helping me deal with a huge amount of hospital data. When difficulties and problems were encountered he was always on hand to advise me and always found time to answer my numerous queries. His help was above and beyond what I could have hoped for.

Thanks also to the Biotechnology and Biosciences Research Council, who kindly funded this research in the form of a DTA studentship awarded to the Department of Biological Sciences, University of Warwick.

Thanks to my committee members, Andrew Price, Laura Green and Kevin Moffat for their assistance and constructive criticism throughout the project. In addition, I would like to thank Matt Keeling for the many snippets of advice given during my PhD.

There are also a number of people who I would like to thank for, at one time or other, finding the time to answer my questions and provide thoughtful advice or suggestions, either during discussions or by email, namely Sheldon Stone, Stephanie Dancer, Martin Bootsma, Stephen Hawkey and Eli Prenecevich. Particular thanks go to Hajo Grundmann, who has dedicated a substantial amount of time to, and interest in, this project. His input, given from such an experienced perspective, has been invaluable.

This thesis would not have been possible without the help of Ben Cooper who was brave enough to let me further develop his model and continue with, what was originally, his research. I have been lucky enough to be able to tap into his encyclopaedic knowledge of the topic a number of times and his counsel has been an enormous help throughout.

Some of the research presented in this thesis was conducted with Charlotte Scarff, an undergraduate student, for her final year dissertation. Having such a keen and diligent student enabled this project to be taken further than would otherwise have

been possible. I am extremely grateful for her involvement and enhancement of the project.

Thanks also go to the Ecology and Epidemiology group with a special mention to Mike Tildesley, Jon Read, Megan Turner and Kay Nolan whose technical advice, support and help has always been appreciated. I would also like to thank Stephen Connor, in the Department of Statistics, for being both a mathematical genius and a pillar of support throughout my time at Warwick.

There are a number of others to whom I am extremely grateful, mainly for helping me keep my sanity and listening to my frequent anxieties. So, heartfelt thanks go to Cathy, Louise, Suzy, Kevin, Jenny, Ian and Ben. Of course the biggest thank you has to go to the much appreciated Christian. Although I am extremely grateful for his help with numerous data analyses and his continual interest in (and opinions on) my work, it is in fact the seemingly endless supply of belief, support and encouragement for which I am indebted.

The final thank you is saved for my family, especially my parents, without their unfaltering faith and unconditional and constant support this PhD would never have been possible. I would like to thank them for just about everything.

# Declaration

All work in this thesis is the result of original research conducted by myself, except where otherwise stated in the text and acknowledgements. The research in Chapter 3 has been previously published (Robotham *et al.*, 2007a) and presented at the 45th ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy), Washington, USA. Some of the research presented in Chapter 2 and the majority of that in Chapter 5 has also been published (Robotham *et al.*, 2007b) and was presented at the Sixth International Conference of the Hospital Infection Society, Amsterdam, Netherlands. No part of this thesis has been submitted for a degree at any other university.

# Summary

This thesis presents research on the epidemiology and transmission dynamics of healthcare-associated infections (HCAI) and focuses on the antibiotic resistant hospital pathogen methicillin-resistant *Staphylococcus aureus* (MRSA).

First, a stochastic mathematical model of MRSA transmission dynamics is developed in which patient movement within and between both hospital and community populations is considered. The effects on transmission of both surveillance and control within this setting are explored. Significant interplay is found to exist between surveillance and control; surveillance is shown to be essential to control success and in addition allows quantification of the level of control achieved. Furthermore, patient movement between hospital and community populations is shown to have a considerable impact on transmission dynamics and on the success of infection control strategies.

Analyses of the demographics of a hospital population using a real hospital dataset are presented and the heterogeneous nature of the patient population described. Differences in admission patterns and length of hospital stay between age groups, gender and speciality are explored. Combining these analyses highlights the patient groups constituting the majority of patient days. Further to this, the heterogeneous nature of patient readmissions is described and the existence of a 'core group' of most frequently readmitted patients is illustrated. Overall, readmissions are found to be far more likely than previously thought, with the majority of patient admissions to hospital being readmissions.

Given this finding of increased readmission, the hospital admission data is used to inform the development of a model in which real patient movements between the hospital and community are simulated and transmission within this setting explored. Endemic behaviour results and the change in movement patterns is found to influence control strategy success. Further to this, the model is extended to simulate transmission within a multi-centre setting where patient movements within a three-hospital and community network are simulated. This increase in heterogeneity within the patient population appears to allow endemic behaviour throughout all hospitals within the network.

# List of Abbreviations

**CA-MRSA** Community-associated methicillin -resistant *Staphylococcus aureus*

**EMRSA** Epidemic methicillin-resistant *Staphylococcus aureus*

**GH** Glenfield General Hospital

**HCAI** Healthcare-associated infections

**HCW** Healthcare worker

**HES** Hospital Episode Statistics

**HISS** Hospital Information Support System

**IBM** Individual-based model

**IQR** Inter-quartile range

**IW** Isolation ward

**LGH** Leicester General Hospital

**LOS** Length of stay

**LRI** Leicester Royal Infirmary

**MRSA** Methicillin-resistant *Staphylococcus aureus*

**NHS** National Health Service

**PBP** Penicillin-binding protein

**PCR** Polymerase chain reaction

**PVL** Panton-Valentine Leukocidin

**UHL** University Hospitals of Leicester

**VRE** Vancomycin-resistant enterococci

**VRSA** Vancomycin-resistant *Staphylococcus aureus*

# Chapter 1

# Introduction

## 1.1 Rationale

Healthcare-associated infections (HCAI) pose an increasing threat to public health. The development of antibiotic resistance by many nosocomial pathogens, such as resistance to methicillin in methicillin-resistant *Staphylococcus aureus* (MRSA), has presented a particular infection control problem with the majority of English acute NHS Trusts being affected (CDSC, 2002) and number of isolate reports increasing (CDSC, 2004). With the emergence of resistance to vancomycin (the current drug of choice for MRSA patients) and the lack of development of alternatives, therapy is fast becoming limited. As a consequence, prevention of infection i.e. infection control, as opposed to therapy once infection has occurred, has become increasingly important.

The aim of this thesis is to further explore the potential for control of HCAI, such as MRSA, using mathematical modelling. By enhancing the understanding of the pathogen's transmission dynamics and by developing quantitative frameworks based on these dynamics, control policies can be investigated. The findings may therefore aid the development of cost-effective and successful infection control strategies (Pelupessy *et al.*, 2002), helping to combat this threat to public health.

## 1.2 Healthcare-associated infections

HCAI are those in which disease is a result of exposure to infectious agents due to healthcare procedures (Grundmann and Hellriegel, 2006). The infections may be caused by a number of transmissible agents such as bacteria, fungi, viruses. parasites or prions and may involve a variety of clinical situations. The most common are those of the urinary tract, accounting for 30-35% of all HCAI. Surgical site infections (for example those at the skin incision, involving foreign implants like joint prosthesis or postoperative bone infection) represent a further 20-30%, with *Staphylococcus aureus* the major pathogen (Huges and Anderson, 2001). Lung infections leading to pneumonia account for 20-25% of HCAI, with the major causative organisms being *Streptococcus pneumoniae* or *Hemophilus influenzae* as well as *S. aureus,* Gram negative enterobacteria and *Pseudomonas aeruginosa*. These infections are often due to ventilator therapy: the weak state of patients coupled with the large amount of tissue involvement leads to high mortality (30%) (Huges and Anderson, 2001). Bloodstream infections account for a further 15%. Catheterisation is the common route of entry for the causative organisms like staphylococci, enterococci or Gram negative bacteria (Aygen *et al.*, 2004). Progression of the bacteraemia to septicaemia or septic shock carries a relatively high mortality rate of 20%. (Huges and Anderson, 2001).

In recent years HCAI have become an increasing risk to public health. It has been estimated that approximately 100,000 new cases occur in England and Wales each year (Glynn *et al.*, 1997). Not only are they associated with an increase in morbidity and mortality of patients they also create logistic and economic problems for healthcare services. As a result, HCAI have recently developed a high public profile; the topic is high on political agendas and has attracted much media attention with MRSA (and more recently *Clostridium difficile* (Starr, 2005)) being regarded as the greatest threat.

### 1.2.1 Why are these infections such a problem?

Since the first applications of antimicrobial chemotherapy to control infections with micro-organisms, the frequency of resistance to antimicrobials by these pathogens has increased. Resistance has developed across groups of micro-organisms: in parasites such as malaria, viruses and the majority of bacterial pathogens (Stewart *et al.*, 1998). Pathogens resistant to antimicrobials commonly used against them obviously present a treatment problem due to the limited effective therapeutic alternatives. Effectively an arms race has ensued; as the pathogen's resistance evolved, new or modified antimicrobial agents had to be developed (Stewart *et al.*, 1998). However, now the development of new antimicrobials is slowing and the pharmaceutical industry is struggling to keep one step ahead of the microbes (Austin and Anderson, 1999a). The rate of introduction of new antimicrobial drugs has slackened making therapeutic options limited (Swartz, 1994); "natural selection" seems to be winning the arms race (Neu, 1992).

As a consequence, resistance is now regarded as a major public health crisis and the evolution of bacteria within hospitals that are multiply resistant to all major antibiotics seems likely (Austin and Anderson, 1999a). It seems clear that a considered comprehensive strategy for antibiotic use is essential, built on a firm understanding of how indiscriminate use translates into the emergence of resistant strains (Levin 2001; Levin and Andreasen, 1999).

So why do these infections flourish in healthcare environments? It is not only the use of broad spectrum antibiotics that make hospitals a favourable environment for the development of resistant strains (Tenover and McGowen, 1996), but also the frequent mixing of patients and healthcare workers (HCW) (Austin and Anderson, 1999a). Studies of various HCAI including vancomycin-resistant enterococci and fungal pathogens have demonstrated transmission via the hands of transiently colonized HCW (Bonten *et al.*, 1996; Sanchez *et al.* 1992). Additionally, patients in healthcare environments are more likely to have open wounds or invasive devices such as catheters and also more likely to be

immunocompromised; making an ideal entry point into an ideal environment for the pathogen.

## 1.3 *Staphylococcus aureus*: a particularly problematic pathogen

*S. aureus* is a Gram positive bacterium that can live harmlessly on many skin surfaces. Humans are a natural reservoir of *S. aureus* and it is commonly carried on the skin or in the nose of approximately 30%-50% of the (healthy) population at any one time (Kluytmans *et al.*, 1997; Lowy, 1998). This asymptomatic, potentially long-term carriage is known as *colonization*, but it is the invasion of staphylococci into the bloodstream; due to a breach in the skin or mucosal barrier that causes *infection* (Lowy, 1998).

Invasive infections, as opposed to colonizations, are usually minor and local causing symptoms such as pimples or boils. However, in some patients the infection may be more serious such as surgical wound infections, pneumonia, bacteraemia with metastatic abscess formation and a variety of toxin-mediated outcomes including gastroenteritis, scalded skin syndrome and toxic shock syndrome (van den Broek, 2003). Most infections can be treated with antibiotics, but the development of antibiotic resistance by *S. aureus* has made treatment a problem in these cases.

### 1.3.1 The development of antibiotic resistance in *S. aureus*

Antibiotics can be used to inhibit growth of many pathogenic bacteria. However, a characteristic of bacterial populations, that they have the potential for rapid evolution, has had a major consequence on the treatment of many HCAI: the emergence and spread of antibiotic resistance (Austin and Anderson, 1999a).

Resistant staphylococci were a clinical problem as early as 1944 when sulphonamide-resistant strains appeared among the wounded during the war (Massad *et al.*, 1993). Penicillin resistance emerged in *S. aureus* in the early

1940s, shortly after its introduction (North, 1946) and by 1948 it was reported that over half of the hospital staphylococcal strains were penicillin-resistant (Barber and Rozwadowska-Dowzenko, 1948). Following this, as new antimicrobial agents were introduced (for example streptomycin, tetracycline, erythromycin and chloramphenicol) resistance to them developed and by the end of the 1950s multiply resistant bacteria were common.

The introduction of methicillin in 1960, a penicillinase-stable antibiotic, seemed to be the answer to these increasing therapeutic problems. However, the relief was short-lived as naturally occurring resistance was reported just a year later. By the late 1960s resistance to methicillin was increasing and a matter of concern within hospitals (Benner and Kayser, 1968). However, the 1970s brought a decrease in the incidence of multiple antibiotic resistance and methicillin resistance declined, but the problem of methicillin resistance had by no means gone for good. By the 1980s new 'epidemic strains' of MRSA appeared. Epidemic MRSA (EMRSA) strains differed from those MRSAs of the 1960s, in that, rather than being plasmid borne, resistance was carried on the chromosome. The first, EMRSA-1 caused outbreaks in London hospitals before spreading beyond (Cooper *et al.*, 2003). Currently in the UK, EMRSA-15 and EMRSA-16 have become widespread since hospital outbreaks in the early 1990's and the emergence of a new strain (EMRSA-17) associated with particularly high resistance has recently been reported (Aucken *et al.*, 2002).

Resistance to methicillin is brought about by an alternative penicillin-binding protein (PBP 2a), coded for by the *mecA* gene, which is unable to bind β-lactam antibiotics such as methicillin (Westran and Struthers, 2003). The *mecA* gene and associated *mec*DNA is acquired through horizontal transfer, (initially as a result of the horizontal transfer of the *mecA* gene from *S. sciuri* (Wu *et al.*, 1996)) and it is the integration of this gene into the chromosome of methicillin-sensitive *S. aureus* that confers resistance (Stefani and Varaldo, 2003). The percentage of a bacterial population that expresses the resistant phenotype varies according to the

environmental conditions (Lowy, 1998) and considerable variations in prevalence exist between institutions and geographic areas (Stefani and Varaldo, 2003).

Despite the fact that alternative antimicrobials that can be used to treat MRSA infections do exist, such as the glycopeptides vancomycin and teicoplanin and the oxazolidone linezolid, with intermediate and even full resistance now being reported (CDC, 2002; Hiramatsu *et al.*, 1997; Howe *et al.*, 1998; Tsiodras *et al.*, 2001) it seems that it is only a matter of time before these too become redundant.

### 1.3.2 Route of transmission

MRSA is almost always spread by direct physical contact i.e. infection is almost invariably acquired by transmission of pre-existing MRSA clones rather than resistance developing *de novo* during antibiotic treatment. The major reservoir of infection consists of both infected and colonized patients and personnel in the hospital (Boyce, 1992; Salgado and Farr, 2003). Transmission of bacterial pathogens by the transiently colonized hands of HCW is well documented (Cookson *et al.*, 1989; Farrell *et al.*, 1998; Grundmann *et al.*, 2002; Salgado and Farr, 2003) and it has been estimated that 80% of HCW who treat MRSA-infected wounds may carry the organism on their hands for as long as three hours (Peacock *et al.*, 1980; Thompson *et al.*, 1982). The bacteria may also be transmitted via contamination of the environment (Bhalla *et al.*, 2004), however the extent of the role the environment plays in transmission is controversial (Hota, 2004) and many studies have shown this role to be limited (Bradley *et al.*, 1991; Cookson *et al.*, 1989; Grundmann *et al.*, 2002).

### 1.3.3 Risk factors for infection

Risk factors for MRSA infection include previous hospitalisation, underlying disease, recent antibiotic use, presence of surgical wounds and catheterisation (Ayliffe *et al.* 1998; Braun *et al.*, 2003; Grundmann *et al.*, 2002; Swartz, 1994). In addition, studies into bed-occupancy, overcrowding and the role of HCW (Blok *et al.*, 2003; Borg, 2003; Nijssen *et al.*, 2003) indicate that greater staff workloads and overcrowding also correspond to an increased risk.

Hospital management itself is therefore linked to many of the potential risk factors. Hospital management has changed dramatically over the past decade: budget restrictions and competition between institutions have created challenges for infection control (Dettenkofer *et al.*, 1999).

Recent studies suggest that the acquisition of MRSA is not restricted to the hospitalised or even to those with predisposing risk factors (Salmeninna *et al.*, 2002) with multiple studies reporting MRSA as a community pathogen (Bukharie *et al.*, 2001; Herold *et al.*, 1998; Pate *et al.*, 1995; Salgado *et al.*, 2003). Recently in the United States, the number of community-associated MRSA (CA-MRSA) infections has increased dramatically (King *et al.*, 2006; Moellering, 2006) and MRSA is now not only being considered as a nosocomial problem. CA-MRSA differ from healthcare-associated MRSA in that CA-MRSA are most commonly still susceptible to non-β-lactam antibiotics and, more worryingly, are correlated to the Panton-Valentine leukocidin (PVL) toxin gene, itself associated with highly lethal necrotizing pneumonia (Naimi *et al.*, 2003; Wannet *et al.*, 2005; Gillet *et al.*, 2002).

### 1.3.4 Epidemiology

Despite the fact that the importance of staphylococci as the major cause of nosocomial infections actually lessened in the early 1960s, to be replaced by enteric Gram negative bacilli, enterococci and fungi (Massad *et al.*, 1993), they are now one of the most important nosocomial infections worldwide. MRSA is widespread and endemic in many UK hospitals (Cooper *et al.*, 2003). In 1990 MRSA accounted for less than 2% of *S. aureus* bacteraemias in the UK, but recent findings show the figure to have increased to approximately 45% by 2005 (Boyce *et al.*, 2005). Furthermore, methicillin-resistant strains, rather than replacing methicillin-sensitive strains, seem to have added to them, further increasing the burden of infection. (Cooper *et al.*, 2004a; Farr, 2004). Moreover, the recent emergence of vancomycin-resistant *S. aureus* (VRSA) implies that the eventual loss of this current drug of choice for MRSA positive patients is inevitable.

Infection with antibiotic resistant organisms has been associated with significantly higher morbidity, mortality and hospital costs than infections caused by susceptible organisms (Salgado and Farr, 2003). The economic impact of MRSA is considerable, with costs associated with increased length of stay, treatment, extra staff etc. The attributable length of stay estimated to be between 2 and 8 days (Abramson and Sexton, 1999; Cosgrove *et al.*, 2005). Each case has been estimated to carry an additional cost of £2500 due to increased patient stay and additional antimicrobial treatment amongst other costs (Mehtar, 1995).

### 1.3.5 Control measures

The lack of treatment options has meant that prevention of infection is all the more crucial; effective infection control is needed to combat the problem. How best to control MRSA remains a controversial matter and the value of infection control strategies often debated (Rahman *et al.*, 2000). As a result, control of nosocomial infections has been attempted using a variety of methods, including: prevention of horizontal transmission, for example through nurse cohorting, patient isolation or increased handwashing compliance of HCW; controlled antibiotic use to inhibit further selection of resistant strains and the implementation of epidemiological surveillance systems including screening programmes. The possibility of vaccination seems unlikely and strategies for developing vaccines are scarce (Balaban *et al.*, 1998). However, despite previously being associated with a number of problems, the potential for use of bacteriophages as therapeutic agents looks promising; further studies still need to be undertaken, but in a setting of ever decreasing antibiotic options phage therapy may be a valuable alternative (Sulakvelidze and Morris, 2001).

As MRSA infection is almost invariably acquired by transmission (particularly via the hands of HCW), rather than developing *de novo*, effective infection control is usually brought about by preventing spread. There are two basic approaches: universal and targeted. Universal approaches, such as increasing hand hygiene, aim to reduce the transmission opportunities between patients, but are not specifically aimed at patients known to be infectious. If they can be implemented

to such an extent that each infectious patient produces (on average) less than one other infectious patient, then this intervention alone is sufficient to control infection within the hospital. In contrast targeted approaches rely on identification of infectious cases through surveillance, and taking steps to reduce their infectiousness from the point of detection.

With infection rates relentlessly increasing, old guidelines for control have become infeasible and impractical to perform. Currently, flexible, targeted approaches, based on medical and scientific rationale and suggestive evidence, tend to be favoured (Ayliffe *et* al., 1998; Cooper *et al.*, 2003). As a consequence strategies are not uniformly applied and vary from hospital to hospital. The endemic state of MRSA in the UK makes control an uphill struggle and coupled with an increasingly aware and demanding public even more pressure has been put on, already overstretched, infection control resources.

Infection control 'bundles', an approach combining many interventions, are currently favoured in the UK. The key to such control methods (as included in the current guidelines (Coia *et al.*, 2006)) is handwashing and a combination of detection and isolation.

- Handwashing

Handwashing is a non-targeted measure that aims to reduce the probability of horizontal transmission through direct physical contact by curtailing the infectious period. Studies have consistently shown that the transient carriage of MRSA on the hands of HCW can be effectively reduced by timely handwashing with liquid soap and water (including Thompson *et al.*, 1982; Peacock *et al.*, 1980, Pittet *et al.*, 2006). However, the efficacy of handwashing is often reduced due to problems attaining and maintaining compliance (Pittet, 2000).

- Isolation

Despite isolation being a pivotal component of most control packages the evidence of its efficacy is contradictory. Cooper and colleagues (2003; 2004b)

describe how the existing narrative reviews differ in their conclusions as to the efficacy of isolation. In view of the apparent lack of systematic assessment they perform a systematic review of the literature and conclude that "no well designed studies exist that allow the role of isolation measures alone to be assessed". However, despite the limitations of existing research they find evidence that concerted interventions that include isolation measures to be able to reduce transmission. Similarly, Mulligan and others (1993), in a consensus review, state that studies examining the impact of strictly-followed isolation measures found a decrease in the incidence of endemic MRSA infection and cross-transmission. From an economic point of view, Jernigan *et al.* (1996) claim that, when studied carefully, the implementation of isolation measures appears to be cost-effective.

- Screening

Screening is used in situations where earlier detection and therefore earlier treatment improves the prognosis of a disease. In terms of HCAI, detection of infection or colonization allows control measures to be imposed upon detected individuals; not only improving the outcome for the individual, but also being beneficial for the population through preventing ongoing transmission to others. Screening may be applied to a whole population (mass) or to particular selected individuals (targeted) and may occur systematically or opportunistically.

MRSA transmission can occur from both colonized and infected patients, therefore both colonized and infected MRSA patients make up the within-hospital reservoir of infection. Infected individuals will most likely be detected through clinical specimens, taken due to overt clinical symptoms such as skin infections like abscesses or boils, or due to systemic infections giving symptoms such as fever, vomiting and diarrhoea. However, if carriage is asymptomatic, no overt clinical symptoms will be present making it unlikely for a clinical sample to be taken. It has been estimated that between 70%-90% of hospitalized patients colonized with MRSA are never identified (Coello *et al.*, 1997; Jernigan *et al.*, 1995). Detecting MRSA in routine clinical samples has been shown to be inadequate and epidemiological surveillance allowing identification and treatment

of carriers is crucial to epidemic control and reduction in infection numbers (Coello *et al.*, 1997; Cookson, 1997; Farr, 2004; Lepelletier, 2004). The importance of this population was highlighted in a study by Thompson *et al.* (1982) in which a hospital MRSA epidemic was controlled only once colonized patients were identified by active surveillance (i.e. in addition to those identified by clinical cultures).

Current screening guidelines

As early detection of carriage of resistant strains is essential for appropriate isolation and effective infection control (Pittet and Waldvogel, 1997), it is clear that some kind of screening of the hospital population is required. Current UK guidelines (Coia *et al.*, 2006) state that at the very least, basic infection control measures should include 'alert' organism surveillance, i.e. the continuous monitoring of specified organism incidence (in this case MRSA) isolated by the microbiology laboratory. Further guidelines depend on the state of MRSA within the hospital and the particular scenario. Where MRSA is endemic the infection control team are advised to continue to assess the occurrence of MRSA and whether most cases are new acquisitions within the hospital or admissions and transfers of already affected patients. The approach in medium to low risk areas where MRSA is endemic includes admission screening of patients who are known to be previously infected or colonized with MRSA, frequent re-admissions or those transferred from high risk populations and potentially the screening of contact cases. In high risk areas these screening activities are expanded so both admission and discharge screening occurs and, in some cases, staff screening. Finally, in an acute hospital with endemic problems it is advised that if a case is identified, detection of colonized or infected patients is carried out on admission, followed by admission to an isolation room or ward until deemed MRSA free.

## Influences on screening success

### *Sample site*

The success of screening seems to be partly dependent on the site sampled. In a study of 403 MRSA carriers, the sensitivity of various sample sites at detecting carriage was found to be 78.5% for sampling from nose alone; 85.6% for nose and throat; 94.3% for nose and perineum and 98.3% for nose, throat and perineum (Coello *et al.*, 1994). The current guidelines state that initially nasal swabs should be taken, following this admission screening, ward screening and screening of staff with positive nasal swabs should include nose, perineum/groin, lesions and manipulated sites (e.g. indwelling intravascular catheters).

### *Sensitivity and Specificity*

As with most medical tests screening is not 100% accurate and may falsely identify both positives and negatives. The sensitivity (proportion of true positive results detected) and specificity (proportion of true negatives) of any test is unlikely to be 100% and there is usually some kind of trade-off between the two, however sensitivity is usually prioritised over specificity.

Therefore, in addition to the site sampled, there is also variability in success due to the particular test used. Recent development of new media (such as CHROMagar) are both sensitive and specific and may aid in the reliable identification of MRSA (Loulergue *et al.*, 2006).

### *Time to detection of resistance*

Clearly the time taken between screening and implementation of control will have an influence on whether a particular screening strategy would be of benefit. If found cost-effective, new advances in rapid diagnostic testing techniques based on immunological or molecular technologies, such as polymerase chain reaction (PCR) assays, may offer a fast and effective alternative to current techniques (Metan *et al.*, 2005; Tenover, 2007).

### 1.3.6 Uncertainties surrounding infection control

With therapeutic options scarce, and becoming scarcer, the focus is shifting to a provision of preventative rather than reactive measures. However, studies on infection control measures are limited (Cooper *et al.*, 2004b) and evidence for their effectiveness sparse and often contradictory (Cooper *et al.*, 2003). Due to this uncertainty over efficacy coupled with the inherent costs and disruption involved, how best to control MRSA remains a much debated matter. Interventions can increase costs to the hospital, increase workloads for staff and disrupt a hospital's working practice and despite some evidence suggesting infection-related costs exceed those of screening and control (Casewell, 1996; Chaix *et al.*, 1999; Cooper *et al.*, 2003; Papia *et al*, 1999), the costs and benefits associated with screening are largely unknown. This may lead to reservations regarding strategy implementation and so it is important, at the hospital level, to be certain the benefits will outweigh these considerable costs and so a greater understanding of the potential benefits is clearly needed.

Performing well-controlled trials of the numerous possible interventions is problematic (Farrington *et al.*, 1998) and, in addition, it is often difficult to determine whether an intervention under trial has been successful, compare relative merits of interventions or identify the reasons for success/failure (Lipsitch *et al.*, 2000). For example, as control policies often comprise many elements many confounders exist, thus making assessment of individual contributions difficult. Similarly, it is sometimes the by-product of an intervention that causes a change in outcome. Furthermore, fluctuations and trends seen ordinarily can be falsely attributed to interventions.

## 1.4 Mathematical modelling

Formulation of a mathematical model which simulates a particular system forces a theoretical framework to be established and thus complex relationships to be brought down to their simplest form. This requires determination of the factors of prime importance and obtaining information on them. This process is not purely mathematical, but relies on clinical medicine also, ensuring the model makes

'biological sense'. This requires an understanding of underlying processes involved (Bonten *et al.* 2001) and, in addition, helps identify areas in which more precise information is needed (Austin and Anderson, 1999a). For example, in terms of antibiotic-resistant pathogens, data on frequency of resistance coupled with drug consumption in a population over time are sparse as well as areas such as the pharmacodynamics of the interaction between drugs and bacteria (Austin and Anderson, 1999a).

Once data are available key parameters can be estimated and used to develop mathematical models, which can then be used for possible scenario analysis, and even theoretical models (in the absence of good data) can help to develop further hypotheses for investigation (Austin and Anderson, 1999a).

Models of infectious diseases aim to simplify the process of disease spread and thus to enhance our understanding of transmission dynamics. These models can apply to all infectious diseases; bacterial, parasitic and viral and mathematical models have already enhanced our knowledge in a number of areas (Bonten *et al.*, 2001). For example, in estimating the impact of HIV, in the design of vaccination programmes (Levin *et al.*, 1999) or in determining effectiveness of infection control measures (Anderson and May, 1991). Models of viral infections in particular have lead to substantial advances in the understanding of disease progression and the effects of therapy (Austin *et al.*, 1998). In terms of bacterial infections, within-host dynamics are less well understood, making mathematical models less common (Levin *et al.*, 1997).

Mathematical models of the transmission dynamics of pathogens provide quantitative predictions and a formal framework, thus allowing assessment of interventions, control measures and criteria for eradication, prior to implementation (Austin and Anderson, 1999a; Austin *et al.*, 1999; Sébille *et al.*, 1997; Sébille and Valleron, 1997). For example Cooper *et al.*, (1999) presented a mathematical model for the spread of hand-borne nosocomial pathogens such as *S. aureus* within a general medical-surgical ward. Simulations of the course of an

outbreak were used to evaluate possible effects of a number of control measures including handwashing and surveillance. In short, models help to quantify the transmission process and effects of infection control (Bonten *et al.*, 2001).

Furthermore, models incorporating economic analyses allow exploration of the cost-effectiveness of control strategies, an important criterion in intervention evaluation. However, few studies have attempted this, examples of those which have addressed putative costs (and cost benefits) involved in infection control include those by Ayliffe *et al.* 1998; Kunori *et al.* 2002; Lauria and Angeletti, 2003 and Vegni *et al.*, 2004.

### 1.4.1 Models of the spread of antimicrobial resistance

As resistance to antimicrobial drugs is now a serious clinical problem in a wide range of infections there is a growing need to understand the factors that lead to the evolution of the spread of resistance. It is likely a combination of pharmacological, genetic, ecological, and social factors are responsible for the patterns of resistance seen and mathematical models of the population dynamics of sensitive and resistant organisms are beginning to provide explanations for these patterns of resistance (Levin *et al.*, 1999).

Mathematical models of the pharmacokinetics of antimicrobial agents (i.e. drug absorption and disposition) can be linked with within-host pathogen population dynamics to give models of the dynamical response of the infectious agent, termed pharmacodynamics. However, the precise pharmacodynamic effects of antibiotic resistance are still uncertain (Austin and Anderson, 1999a). Many models of bacterial pathogens focus, instead, on the development and spread of antimicrobial resistance within the bacterial population for example in a study by Austin and Anderson (1999a) mathematical modelling is used to address the issue of resistance at a number of levels: within the host, within and between hospital settings as well as the epidemiology and evolution in communities of people. Mathematical modellers can use such frameworks to address questions such as whether tailoring drug use/ decreasing treatment rate will sufficiently decrease the

frequency of resistant microbes (Austin and Anderson, 1999a; Stewart *et al.*, 1998).

Studies by Massed *et al.* (1993) and Bonhoeffer *et al.* (1997) address the population dynamics of organisms such as *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae*, i.e. organisms that cause disease, leading to clearance upon antibiotic treatment. The first group, Massad *et al.* (1993) find that antibiotic treatment creates a selective pressure causing a shift in the outcome of competition between sensitive and resistant strains. While Bonhoeffer *et al.* (1997) find that, in most cases, the most beneficial antibiotic strategy in terms of minimizing resistance is to treat with combinations of antibiotics. However, they note that the spread of resistance due to treatment will be faster than the decrease of resistance through removal of treatment, a result which agrees with the results of other resistance models (Anderson and May, 1991).

The studies by Levin *et al.* (1997) and Stewart *et al.* (1998) also address the development of resistance, but differ in that the bacteria they study have the capability of asymptomatic, long-term colonization. Many of the organisms causing nosocomial infections, e.g. *Streptococcus pneumoniae*, *S. aureus*, *Enterococcus* spp., and *Escherichia coli,* are of this kind, where disease only occurs when the (normally commensal) bacteria enter a sterile site (Bonhoeffer *et al.*, 1997). Models for these types of bacterial infection also suggest that in order to deal with the problem of antibiotic resistance an understanding of the population dynamics of both sensitive and resistant strains is crucial.

Few studies combine population genetics issues, which determine the evolution and spread of resistant organisms, with the transmission dynamics in host populations (Austin *et al.*, 1999; Bonhoeffer *et al.*, 1997; Levin *et al.*, 1997; Sébille *et al.*, 1997). It seems that an interdisciplinary approach is required to understand resistance evolution and spread, and so too to understand how best to manage it (Austin and Anderson, 1999a; Stewart *et al.*, 1998).

### 1.4.2 Models of the transmission and control of HCAI

Despite the uncertainty over how best to control hospital pathogens very few of the multitude of studies on infection control methods provide a quantitative measure of practical efficacy (Bonten *et al.* 2001). In terms of nosocomial pathogens, mathematical models can help give reasons for observed patterns and the increased understanding of their dynamics means theoretical guidelines can be provided for the design and development of cost-effective and successful infection control strategies ( Grundmann and Hellriegel, 2006; Pelupessy *et al.*, 2002).

Models of infectious disease transmission commonly fall into one of two categories: deterministic or stochastic. Deterministic models use differential equations to approximate the mean behaviour from a set of initial conditions. The main advantage of this 'analytical' approach is generality (Bonten *et al.* 2001). In contrast, stochastic models define movements of individuals to be chance events occurring at random time intervals determined by the assumed model parameters. A stochastic model simulates transmission given those parameter values and as chance events are captured, the outcome will be different for different simulation runs. An advantage of this type of model is therefore that the range of possible outcomes that may occur can be seen, accounting for the effect of random fluctuations (Bonten *et al.* 2001). A disadvantage, however, is that the outcome is only applicable to the parameter values chosen (Bonten *et al.* 2001).

Due to the small number of patients in a hospital population, particularly single wards, chance or stochastic effects may have a large influence on the transmission dynamics (Grundmann and Hellriegel, 2006) and therefore stochastic models are generally thought to be the most appropriate for modelling HCAI.

In the past 7 or 8 years there have been a number of mathematical models looking specifically at nosocomial infection transmission dynamics, providing testable hypotheses and allowing quantitative assessment of infection control in both hospitals and communities (Austin and Anderson, 1999a; Austin and Anderson, 1999b; Austin *et al.*, 1999; Bonten *et al.*, 2001; Cooper *et al.*, 1999; Cooper *et al.*,

2003; Cooper *et al.*, 2004a; D'Agata *et al.*, 2002; Grundmann *et al.*, 2002; Levin, 2001; Lipsitch *et al.*, 2000; Sébille *et al.*, 1997; Sébille and Valleron, 1997).

The earliest models of HCAI concentrated on transmission dynamics within a single hospital ward (Austin *et al.*, 1999; Cooper *et al.*, 1999; D'Agata, *et al.*, 2002; Sébille *et al.*, 1997). Cooper *et al.* (1999) use a single ward model to investigate the effects of handwashing and reducing the number of colonized admissions. A reduction in MRSA spread is shown by both strategies. In addition, their results highlight the effects of stochasticity on transmission events. Similarly Austin *et al.* (1999) use a single ward model to investigate control measures on the prevalence of vancomycin-resistant enterococci (VRE). The framework of this model is based on those of vector-borne diseases (i.e. using the Ross-MacDonald equations (Anderson and May, 1991)) in that the HCW are viewed as vectors and patients definitive hosts. They find hand hygiene and nurse cohorting to be effective control methods, although the constant introduction of VRE colonized patients allowed endemicity. Grundmann *et al.* (2002) made use of this model in the context of MRSA transmission and find staffing levels to be of critical importance.

Sébille *et al.* (1997) propose a deterministic single ward model in which MRSA transmission occurs through patient and staff contact. Both hand disinfection and antibiotic use were explored. They found that the number of patients being colonized by strains from HCW was crucial to the transmission dynamics, whilst both hand hygiene and antibiotic policy showed surprisingly little effect. Curtailing admission of colonized patients however, allowed rapid eradication of the pathogen.

Sébille and Valleron (1997) also use a stochastic approach to simulate the spread of an antibiotic-resistant pathogen. They use a Monte Carlo simulation in which every patient and staff member is represented, such that heterogeneities between individuals can be considered. In this study they highlight the importance of

handwashing and the role of admitted colonized patients in the initiation and perpetuation of outbreaks.

## 1.5 An overview of the thesis

### Modelling HCAI transmission dynamics and infection control

In Chapter 2 the development of a stochastic mathematical model describing the transmission of a HCAI, in and between hospital and community populations, is presented. At present, most models of the transmission dynamics of MRSA and HCAI have addressed only transmission either within the hospital (such as work by Bonten *et al.*, 2001; Grundmann *et* al., 2002 and Sébille *et al.*,1997) or, more rarely, within the community (Bukharie *et* al., 2001; Leman *et al.*, 2004; Salgado *et al.*, 2003). However, it seems likely that heterogeneity of the population will influence dynamics considerably (Cooper *et al.*, 2003) and therefore needs to be considered in infection control efforts (Smith *et al.*, 2004). Therefore it can be seen that the inclusion of the movement patterns of individuals between the hospitals and the community are necessary.

In Chapter 3 this model will be used to assess the impact of infection control measures. Both surveillance (patient screening) and control (an isolation ward) are examined, and the interplay between the two investigated.

### Using data to inform the model

Demographics of the patient population are important to the transmission dynamics of HCAI as they define the context in which infection is acquired. Despite the existence of a wealth of data there is little published on the demographics of patient populations within hospitals. In Chapter 4 hospital admission data is used to describe patient demographics of a hospital population over a seven year period.

The University Hospitals of Leicester (UHL) NHS Trust was used for the purposes of this study. The Trust comprises three hospitals: Leicester Royal

Infirmary, Leicester General Hospital and Glenfield General Hospital, which collectively have a catchment area of approximately 1 million people across the city of Leicester, and the counties of Leicestershire and Rutland. The Trust is the main provider of secondary and tertiary healthcare in this region and consequently the majority of hospitalisations within the community occur within the Trust.

Despite the potential importance of the community population to the transmission dynamics of HCAI, to the author's knowledge, there are no studies describing movements to and from the hospital and community. An increased knowledge of the patient population, such as the proportion of patients likely to come back into hospital after discharge, how many times they are likely to admission hospital, how long it is likely to be between each admission, how long they are likely to spend in hospital on each admission and so on, may provide insight into HCAI transmission. An increased understanding of such movement patterns, in turn allowing increased understanding of HCAI such as MRSA and *C. difficile*, would provide a better basis from which to design control strategies. Under this rationale, Chapter 5 investigates the readmission patterns of the patient population at the UHL NHS Trust.

Chapter 6 further extends the model of HCAI transmission dynamics developed in Chapters 2 and 3 to simulate transmission in a setting of realistic patient movement patterns based on those for the UHL NHS Trust presented in Chapters 4 and 5. Again, the impact of surveillance and control strategies are assessed.

**Developing a multi-centre model of HCAI transmission dynamics**

As the UHL NHS Trust data includes (and distinguishes between) admissions for the three hospital sites that comprise the Trust, patient movement patterns around a multi-centre healthcare system can be established. Using these movement patterns, in Chapter 6 a three hospital model is developed and transmission dynamics within a multi-centre setting investigated.

# Chapter 2

# Developing a mathematical model of MRSA transmission dynamics

This chapter demonstrates the use of mathematical models as a tool for further understanding infection transmission dynamics and subsequently their use in theoretical assessment of control strategies. Firstly the framework of a model of HCAI transmission dynamics is described. Following this is the extension of this model such that effects of infection control strategies can be considered. An analytical exploration of this system is presented in which factors influencing transmission dynamics are investigated, in addition the results of a deterministic version of the model are presented. Some of the research included in this chapter is published (Robotham *et al.*, 2007b) and has previously been presented at the Sixth International Conference of the Hospital Infection Society, Amsterdam, Netherlands. Where indicated (in the figure legends) research has been undertaken in collaboration with C.A. Scarff.

## 2.1 Model rationale

Most models of the transmission dynamics of MRSA and HCAI have addressed only transmission either within the hospital (such as those studies outlined in Chapter 1) or, more rarely, within the community (Bukharie *et* al., 2001; Leman *et*

*al.*, 2004; Salgado *et al.* 2003). However, heterogeneity of the population may influence dynamics considerably (Cooper *et al.*, 2003).

It seems intuitive that in studying HCAI focus should be on the hospital, with carriage and transmission in the community being largely ignored, especially for such pathogens as MRSA where the colonization of healthy people is generally harmless. However, the recent work by Cooper *et al.* (2003 and 2004a) and Smith *et al.* (2004) highlights the importance of considering the heterogeneous nature of the population in infection control efforts. These studies indicate that movement of carriers between hospitals, long-term care facilities and the community may play a large part in determining the dynamics of pathogenic spread. Upon consideration of heterogeneities the predicted dynamics become consistent with reported epidemic patterns (in the form of fast and slow phases). Similarly, a recent model by Cooper *et al.*, (2004a) suggests that the interaction between hospital and community may produce different long and short-term dynamics and may explain many of the epidemiological features of the transition from epidemic (short, limited outbreaks) to endemic (persistent) behaviour.

Therefore it can be seen that studies including the development of contact networks describing movement patterns of individuals between hospitals and between the hospital and the community are necessary. The inclusion of 'hospital demography' (i.e. a network structure) will allow the transmission dynamics of MRSA to be modelled *considering* heterogeneity.

In view of this, this work builds on studies, particularly those by Cooper *et al.* (1999; 2003; 2004a) which use stochastic models to explore the spread of nosocomial pathogens, and the model described here simulates transmission within and between hospital and community populations.

## 2.2 Description of model framework

The framework is based closely on Cooper *et al.* (1999; 2003; 2004a). A closed population is modelled consisting of both a fixed size hospital and the community

it serves. Individuals in both the hospital and community populations are categorised as either MRSA-positive and infectious (either infected or colonized) or MRSA-negative and susceptible to infection (for brevity referred to as infected and susceptible respectively from now on).

Infected inpatients are classified into one of three groups: isolated (ISO); detected but not isolated (DNISO) or undetected infected ($UI_H$). Isolated patients are those known to be MRSA-positive and consequently placed in an isolation facility; detected but not isolated patients are those known to be positive, but who cannot be isolated; and undetected infected patients are those not known to be infectious. The term isolation considers any mechanism by which patients are effectively isolated in terms of transmission; this might include specific facilities (e.g. an isolation ward) or staff (e.g. cohort nursing). For convenience, isolation ward (IW) is used as the abbreviation for this facility. The key assumptions are that isolation is perfect (i.e. transmission from isolation never occurs) and it is limited (i.e. there is a fixed capacity in terms of the numbers of patients that can be isolated at any one time). Infected patients are detected, and isolated if capacity is available (if the fixed capacity of IW is not reached), and marked DNISO otherwise. Thus, observed (apparent) hospital prevalence of infection (i.e. those picked up by any detection effort) is ISO + DNISO, whereas the actual (real) prevalence is ISO + DNISO + $UI_H$.

Under the assumption of 100% bed occupancy, patients discharged from hospital are immediately replaced by an individual from the community, with the rate of discharge ($\mu$) being assumed equal for all hospital subgroups (i.e. regardless of infection status).

The community population is also split into sub-groups, each with a different readmission rate. Upon discharge patients enter the first community group ($C_1$) which has a high readmission rate ($\theta_1$) from where, if they are not readmitted, they move at a set rate ($\delta$) to the second community group ($C_2$) with a lower readmission rate ($\theta_2$) (Cooper *et al.*, 2003; Cooper *et al.*, 2004a). The number of

susceptible and infected individuals in $C_1$ and $C_2$ are denoted $S_{C1}$, $I_{C1}$, $S_{C2}$ and $I_{C2}$ respectively. On admission or discharge an individual would join the corresponding group (i.e. susceptible or infected) within the hospital or community population respectively.

Transmission is assumed to be within the hospital only, meaning the dynamics are hospital driven. The rate of infection of susceptible patients is determined by the transmission parameter $\beta$ and the proportion of $UI_H$ and DNISO patients, i.e. isolated patients do not contribute to infection, and for simplicity it is assumed that $UI_H$ and DNISO patients are equally infectious. Homogeneity is assumed within the susceptible population with all individuals having an equal chance of becoming infected. For simplicity, recovery of infected patients is assumed to occur at an equal rate ($\gamma$) for all infected groups in both the hospital and community, and isolated patients are assumed not to recover, but be discharged infected. However, the effects of eradication therapy may mean that in fact the recovery rate for known infected (and therefore treated) patients would be greater than for untreated patients (i.e. undetected infected and infecteds in the community). Additionally, homogeneity of MRSA itself is assumed in terms of both transmissibility and detectability.

### 2.2.1 Including screening as an infection control strategy

Within this setting, of HCAI transmission within and between hospital and community populations, two screening strategies are considered: random and on-admission. Both strategies are assumed to be 100% accurate and the effects of sensitivity and specificity are not included explicitly, although their effects can be included in the model parameters.

Random screening allows patients to enter the hospital unscreened as either susceptible ($S_H$) or undetected infected ($UI_H$). Routine random screening then occurs at a set rate ($\phi$), so that each patient is screened at an average interval of $1/\phi$ days. Detected infections are moved into the IW. If the IW is at capacity then

these detected patients are DNISO and have priority to move into IW when space becomes available, i.e. when an isolated patient is discharged.

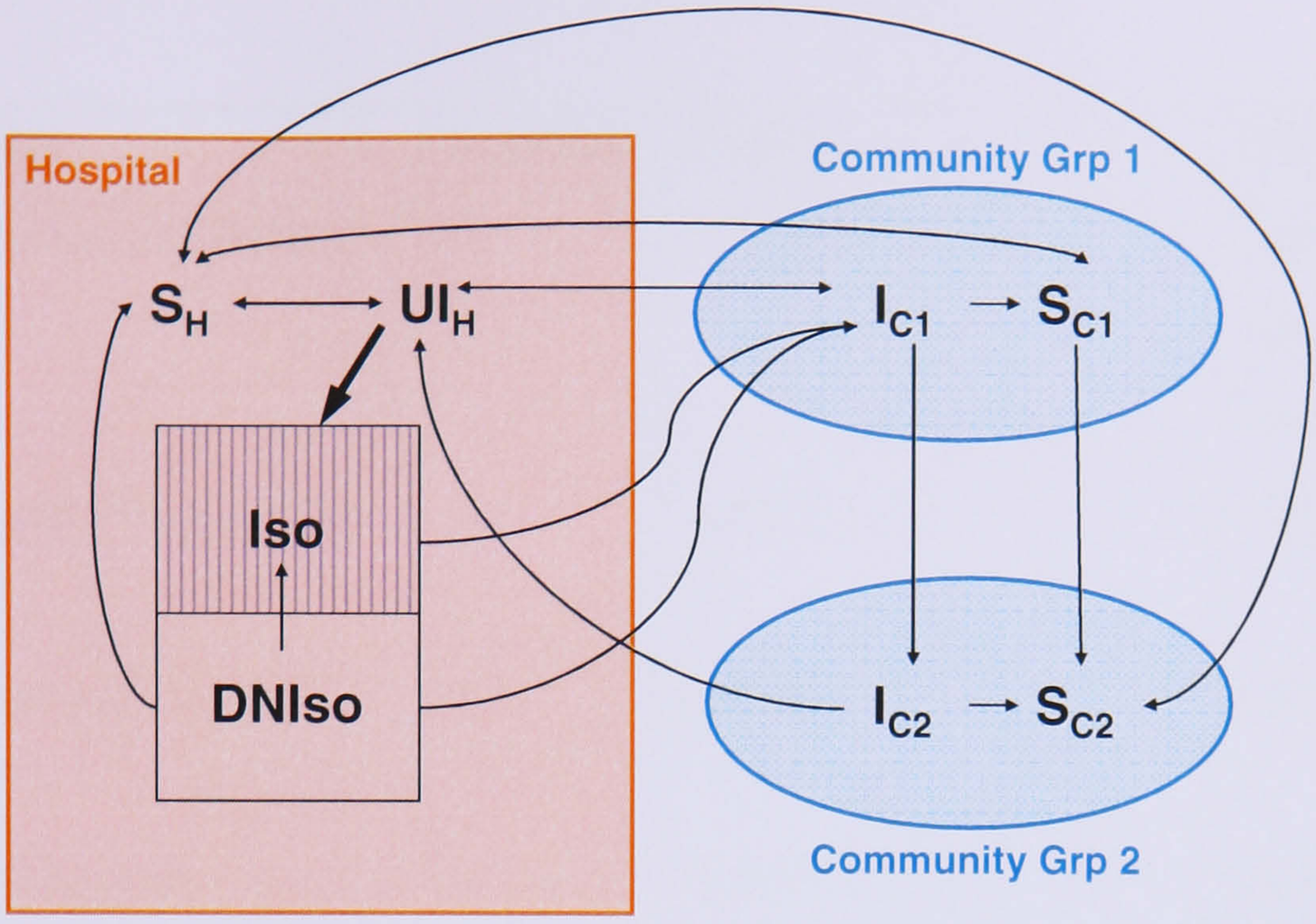
The on-admission screening strategy screens a proportion (ω) of patients on entry to the hospital, so detected infected individuals are placed directly in isolation and cannot infect. Again, if the IW is at capacity then detected infected patients become DNISO. Note that a proportion (1-ω) of admissions are unscreened and join $S_H$ or $UI_H$ appropriately, where they will remain, unscreened, for the duration of their stay.

To allow effective comparison between the two strategies the numbers of patients screened per day were set to be equal. The number screened at random is ϕN per day (where N is hospital capacity) and admission rate is μN per day (where 1/μ is average length of stay) so that the numbers screened on-admission per day are ωμN. For the screening effort to be equal:

$$\phi = \omega\mu$$

Schematic diagrams of the model framework including the two screening strategies are presented in Figure 2.1, although the model framework allows both strategies to be included simultaneously.

a. Random screening




b. On-Admission screening

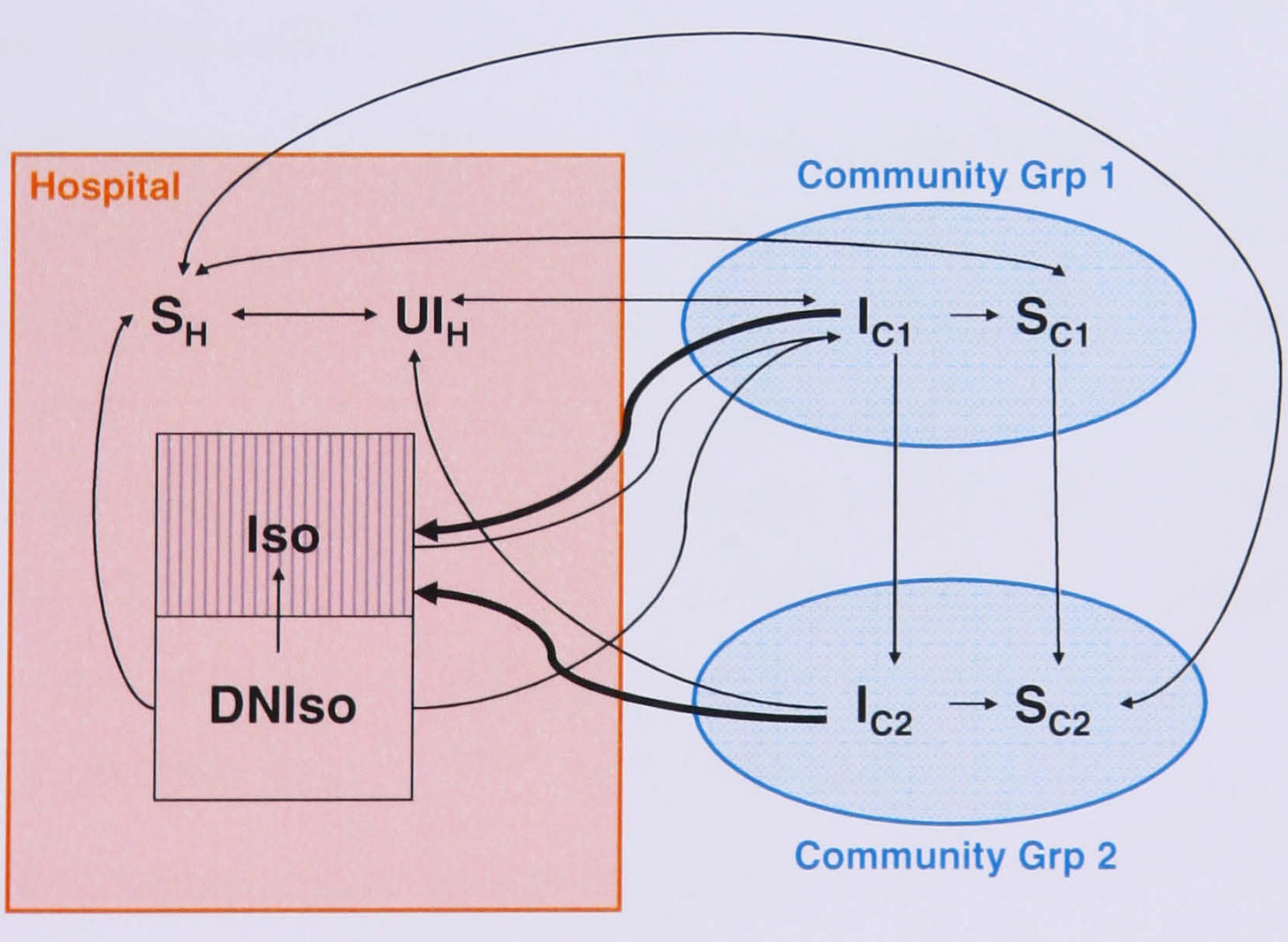



**Figure 2.1** Schematic diagram of the model for both screening strategies: (a) random screening and (b) screening on-admission. See text for symbol definitions. The bold lines indicate the screening processes. Parameter values determining rates of transitions between states are given in Table 2.1. The events the arrows represent are given in Table 2.2.

Parameter values are in accordance with previous work by Cooper *et al.* (2003; 2004a) and given in Table 2.1.

| **Parameter** | **Symbol** | **Value** | **Reference** |
|---|---|---|---|
| Transmission coefficient | $\beta$ | 0.1622 | Defined by other parameters to set value of $R_0$ |
| Discharge/admission rate ($day^{-1}$) | $\mu$ | 0.125 | (Cooper *et al.*, 2003) |
| Recovery rate ($day^{-1}$) | $\gamma$ | 0.0027 | (Cooper *et al.*, 2003) |
| Readmission rate – community group 1 | $\theta_1$ | 0.0057 | (Cooper *et al.*, 2003) |
| Readmission rate – community group 2 | $\theta_2$ | 0.00063 | (Cooper *et al.*, 2003) |
| Decay rate from community group 1 to 2 | $\delta$ | 0.03 | (Cooper *et al.*, 2003) |
| Community group 1 population size | $C_1$ | Range: $3.3263 \times 10^3$ – $3.5014 \times 10^3$ | Defined by other parameters |
| Community group 2 population size | $C_2$ | Range: $1.584 \times 10^5$ – $1.6673 \times 10^5$ | Defined by other parameters |
| Overall community population size | C | Range: $1.6172 \times 10^5$ - $1.70236 \times 10^5$ | Defined by other parameters: $C_1 + C_2$ |
| Isolation ward capacity | NISO | Range: 0 – 50 | - |
| Hospital population size | NH | 1000 – NISO | - |

**Table 2.1** Parameter values used in the model

The model proceeds as a stochastic, iterative process with successive events performed after random time intervals (drawn from a negative exponential distribution with rate given by the total rate of events) and events occurring to whole individuals. This stochastic nature of the model is essential for the simulation of dynamics of hospital infections, where random events have the potential to greatly influence outbreak behaviour (Cooper *et al.*, 1999). Replication of each simulation is necessary as each simulation run will lead to a different outcome. Unlike all other events, the movement of susceptible individuals from $C_1$ to $C_2$ is assumed to be deterministic due to the large numbers of individuals involved. All stochastic events and their corresponding rates are listed in Table 2.2.

At the start of each simulation it is assumed that the hospital is an entirely susceptible population and that all infected individuals are in the community, therefore an epidemic can only occur once an infected individual is admitted to hospital. The size of the community population is set to be 170230, calculated from the other parameter values in a setting without infection, using the following equations:

$$\dot{C}_1 = \mu NH - \theta_1 C_1 - \delta C_1 \tag{2.1}$$

and

$$\dot{C}_2 = \delta C_1 - \theta_2 C_2 \tag{2.2}$$

giving the equilibrium value for community group 1,

$$C_1^* = \frac{\mu NH}{\theta_1 + \delta} \tag{2.3}$$

and the equilibrium value for community group 2 as,

$$C_2^* = \frac{\delta \mu N H}{\theta_2(\theta_1 + \delta)} \tag{2.4}$$

Out of this community population it is assumed that 100 individuals are initially infected.

The model was written and run in MATLAB® (Version, 7.0, MatLab, The MathWorks, Natick, MA, USA) on a personal computer.

| Event description | Event Rate | Event |
|---|---|---|
| Infection of a susceptible within the hospital | $\beta S_H (UI_H + DNISO)$ | $S_H \rightarrow UI_H$ |
| Recovery of an undetected infected within the hospital | $\gamma UI_H$ | $UI_H \rightarrow S_H$ |
| Detection of an undetected infected in the hospital (i.e. by random screening)* | $\phi UI_H$ | $UI_H \rightarrow ISO$ ** <br> $UI_H \rightarrow DNISO$ ** |
| Recovery of a DNISO | $\gamma$ DNISO | DNISO $\rightarrow S_H$ |
| Discharge of an isolated patient (and their replacement by a DNISO)* | $\mu$ ISO | ISO $\rightarrow I_{C1}$ and <br> DNISO $\rightarrow$ ISO *** |
| DNISO discharged* | $\mu$ DNISO | DNISO $\rightarrow I_{C1}$ |
| Susceptible discharged* | $\mu S_H$ | $S_H \rightarrow S_{C1}$ |
| Undetected infected discharged* | $\mu UI_H$ | $UI_H \rightarrow I_{C1}$ |
| Admission of susceptible from community group 1 | $\frac{C_1\theta_1}{C_1\theta_1 + C_2\theta_2} \frac{S_{C1}}{S_{C1} + I_{C1}}$ | $S_{C1} \rightarrow S_H$ |
| Admission of susceptible from community group 2 | $\frac{C_2\theta_2}{C_1\theta_1 + C_2\theta_2} \frac{S_{C2}}{S_{C2} + I_{C2}}$ | $S_{C2} \rightarrow S_H$ |
| Admission of infected from community group 1; unscreened | $1-\omega \frac{C_1\theta_1}{C_1\theta_1 + C_2\theta_2} \frac{I_{C1}}{S_{C1} + I_{C1}}$ | $I_{C1} \rightarrow UI_H$ |
| Admission of infected from community group 1; screened and detected | $\omega \frac{C_1\theta_1}{C_1\theta_1 + C_2\theta_2} \frac{I_{C1}}{S_{C1} + I_{C1}}$ | $I_{C1} \rightarrow ISO$ ** <br> $I_{C1} \rightarrow DNISO$ ** |
| Admission of infected from community group 2 - unscreened | $1-\omega \frac{C_2\theta_2}{C_1\theta_1 + C_2\theta_2} \frac{I_{C2}}{S_{C2} + I_{C2}}$ | $I_{C2} \rightarrow UI_H$ |
| Admission of infected from community group 2 - screened and detected | $\omega \frac{C_2\theta_2}{C_1\theta_1 + C_2\theta_2} \frac{I_{C2}}{S_{C2} + I_{C2}}$ | $I_{C2} \rightarrow ISO$ ** <br> $I_{C2} \rightarrow DNISO$ ** |
| Movement of an infected from community group 1 to community group 2 | $\delta I_{C1}$ | $I_{C1} \rightarrow I_{C2}$ |

*** Each discharge event/movement into IW is associated with an admission event (of either a susceptible or infected individual from one of the two community groups).**

**** This event can only occur given that at least one DNISO patients exists.**

**Table 2.2** Stochastic events and event rates.

## 2.3 The model in terms of $R_0$

The transmissibility of the infection is considered in terms of the basic reproduction number ($R_0$), defined as the average number of secondary cases caused by one primary case in a completely susceptible population. Using this definition in a scenario where $R_0$ is above 1 an epidemic will ensue, whereas an $R_0$ less than one will not cause epidemic behavior. Therefore the aim of any infection control practice is to reduce $R_0$ to less than 1.

### 2.3.1 Analytical description

For models, such as this, where the community population is included explicitly, there are two components to $R_0$: a within-hospital value ($r_0$) and a term to include the possibility of multiple returns to hospital (Cooper, *et al.*, 2003; Cooper *et al.*, 2004a). Readmissions (i.e. multiple returns to hospital) have the potential to reintroduce infection and may be sufficient to cause an epidemic, especially if the infected individual is brought into an entirely susceptible population. This reintroduction of infection into the hospital, by an infected person readmitted from the community can be measured in terms of P, the probability of an infected patient being readmitted while still infected. Using a reproductive number that considers the term P allows transmission to be spread over multiple visits.

The within-hospital reproduction number in the absence of intervention, given by

$$r_0 = \frac{\beta}{\mu + \gamma}, \tag{2.5}$$

considers only the number of secondary cases arising from a single admission. The overall $R_0$ considers the number of secondary cases caused by a single visit and the mean number of visits per patient, while they are still infected (Cooper, *et al.*, 2003; Cooper *et al.*, 2004a).

If P is the probability that an infected patient is discharged and readmitted while still infected (in the absence of control), then 1/(1-P) is the mean number of infected visits. For example, if there were a 50% chance of being discharged and

readmitted while still infected (i.e. P = 0.5) you would expect two admissions whilst infectious.

So that

$$R_0 = r_0 \frac{1}{1-P}, \qquad (2.6)$$

where

$$P = \frac{\mu\theta_1(\theta_2+\gamma)+\mu\delta\theta_2}{(\theta_1+\gamma+\delta)(\theta_2+\gamma)}. \qquad (2.7)$$

Therefore $R_0$ can be expressed as

$$R_0 = \frac{\beta(\theta_1+\gamma+\delta)(\theta_2+\gamma)}{(\mu+\gamma)((\theta_1+\gamma+\delta)(\theta_2+\gamma)-\mu\theta_1(\theta_2+\gamma)-\mu\delta\theta_2)}. \qquad (2.8)$$

The value for $r_0$ (within-hospital) was taken from the study by Cooper *et al.* (2003; 2004a) and set at 1.27 and the value of P was calculated to be 0.037 using the parameter values shown in Table 2.1 (taken from the same study), these parameters give an overall $R_0$ value of 1.32.

**Including screening as an infection control strategy**

Including control by isolation (but not any constraint on isolation capacity) has differing impact depending on the screening strategy adopted. Random screening has the effect of curtailing the period of time over which infected individuals can transmit (i.e. they are removed from general circulation). If $r_0'$ is the within-hospital reproduction number with random screening, then

$$r_0' = \frac{\beta}{\mu+\gamma+\phi}. \qquad (2.9)$$

Whereas, when patients are screened on admission, the effect is to reduce P to $P'$ where

$$P' = (1-\omega)P. \qquad (2.10)$$

### 2.3.2 Analytical results

#### Comparing random and on-admission screening

The properties of each strategy can be described in terms of overall and within-hospital $R_0$ values given different levels of surveillance effort. Figure 2.2 (a) shows a diagrammatic representation of $R_0$ values and compares both the within-hospital $r_0$ and the overall $R_0$ for the two screening strategies.

Upon an increase in surveillance effort, random screening gives a decrease in within-hospital $r_0$ and the overall $R_0$ value decreases at the same rate. Random screening has no effect on the readmission of community infection. The decrease in the overall $R_0$ is simply due to the hospital $r_0$ effects. Conversely, screening on admission has no effect on the within-hospital $r_0$ and the decrease in the overall $R_0$ corresponds only to the decrease in infectious readmissions from the community (1/(1-P)).

For these initial conditions (Figure 2.2 (a)), it is the reduction in $r_0$ as opposed to the reduction in 1/(1-P) that is likely to influence the transmission dynamics to the greatest degree and therefore random screening is the strategy best able to reduce $R_0$; only random screening is able to reduce $R_0$ to less than 1.

#### Consideration of setting: the effect of reproductive number and readmission rate

Figure 2.2 (b) shows overall and within-hospital $R_0$ values in a setting of increased infected patient movement between the hospital and community populations (i.e. P has increased, from 0.037 to 0.5). Under these initial conditions as screening effort increases the reduction in 1/(1-P) by on-admission screening follows a similar pattern to the reduction in $r_0$ by random screening. Therefore both strategies have approximately the same ability to reduce overall $R_0$. An increase in P has effectively increased the benefit obtained through on-admission screening.

The bottom two panels of Figure 2.2 (c and d) again compare settings of low and high readmission rates. However, in these cases the initial condition for within-hospital $r_0$ is reduced to be less than 1 (such that a hospital epidemic will die out in the absence of infected admissions). In a setting where P is low, the reduction in initial $r_0$ has the result of enabling the overall $R_0$ to be brought below one by on-admission screening at high screening efforts; however, the reduction in $r_0$ is still of greatest importance to the transmission dynamics and $R_0$ is still reduced further by random screening. When P is substantially increased, however, the relationship between screening effort and 1/ (1-P') again becomes non-linear and the influence of on-admission screening on overall $R_0$ is increased.

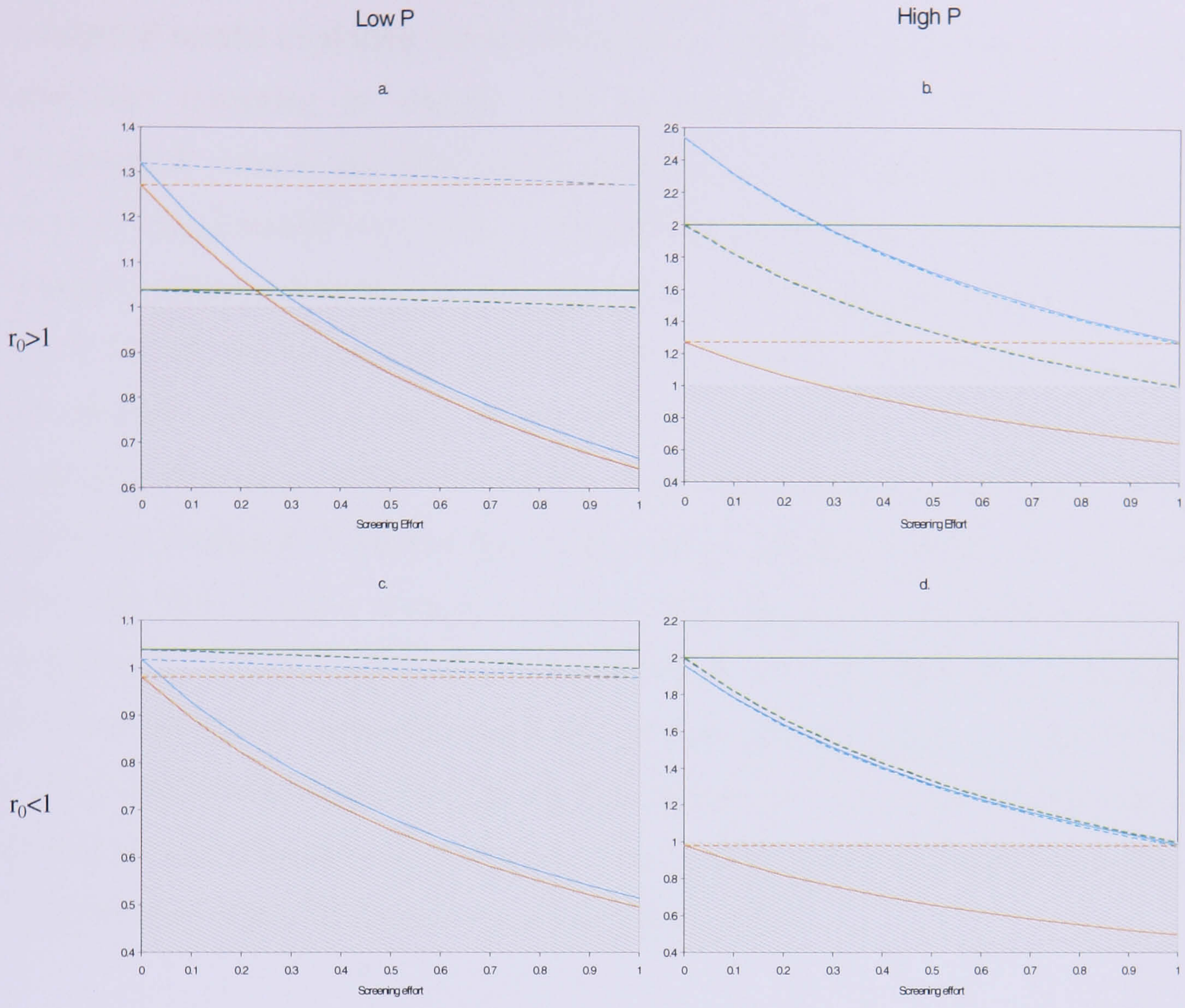



**Figure 2.2** Diagrammatic representations of $r_0$, $R_0$ and 1/(1-P) values given different screening effort levels and initial conditions. Full lines (—) denote random screening and dashed lines (---) screening on-admission. The orange lines show within-hospital $r_0$ values, green lines 1/(1-P) values and light blues overall $R_0$ values. Shaded grey areas indicate the region where reproduction numbers are less than 1, i.e. control occurs. Initial conditions: (a) $R_0 = 1.32$, $r_0 = 1.27$, $P = 0.037$; (b) $R_0 = 2.54$, $r_0 = 1.27$, $P = 0.5$; (c) $R_0 = 1.01$, $r_0 = 0.98$, $P = 0.037$; (d) $R_0 = 1.96$, $r_0 = 0.98$, $P = 0.5$. In all panels $\phi$ = range: 0-0.125, $\omega$ = range: 0-1 to create screening efforts from 0 to 1.

## Combining random and on-admission screening

Analytical results exploring the effectiveness of combinations of random and on-admission screening in settings with increasing infective readmissions (i.e. increasing P values) are displayed in Figure 2.3. The most effective ratio of random: on-admission screening is dependent on the degree of movement by infectious patients between the hospital and community populations (i.e. P). For low P (<0.35) random screening alone provided greatest control. As P increases the greatest level of control results from a combination of strategies with gradually decreasing levels of random screening and increasing levels of on-admission screening. Therefore in a setting where infected readmissions are more likely, the most effective strategy focuses on reducing the chance of these infected readmission episodes and thus predominantly on on-admission screening. However, at high P values the most effective screening strategy was not that of 100% on-admission screening: 0% random screening, but instead a combination of random and on-admission screening. Also as P increases the ability to control decreases (note the differences in scale on the $R_0$ axes).

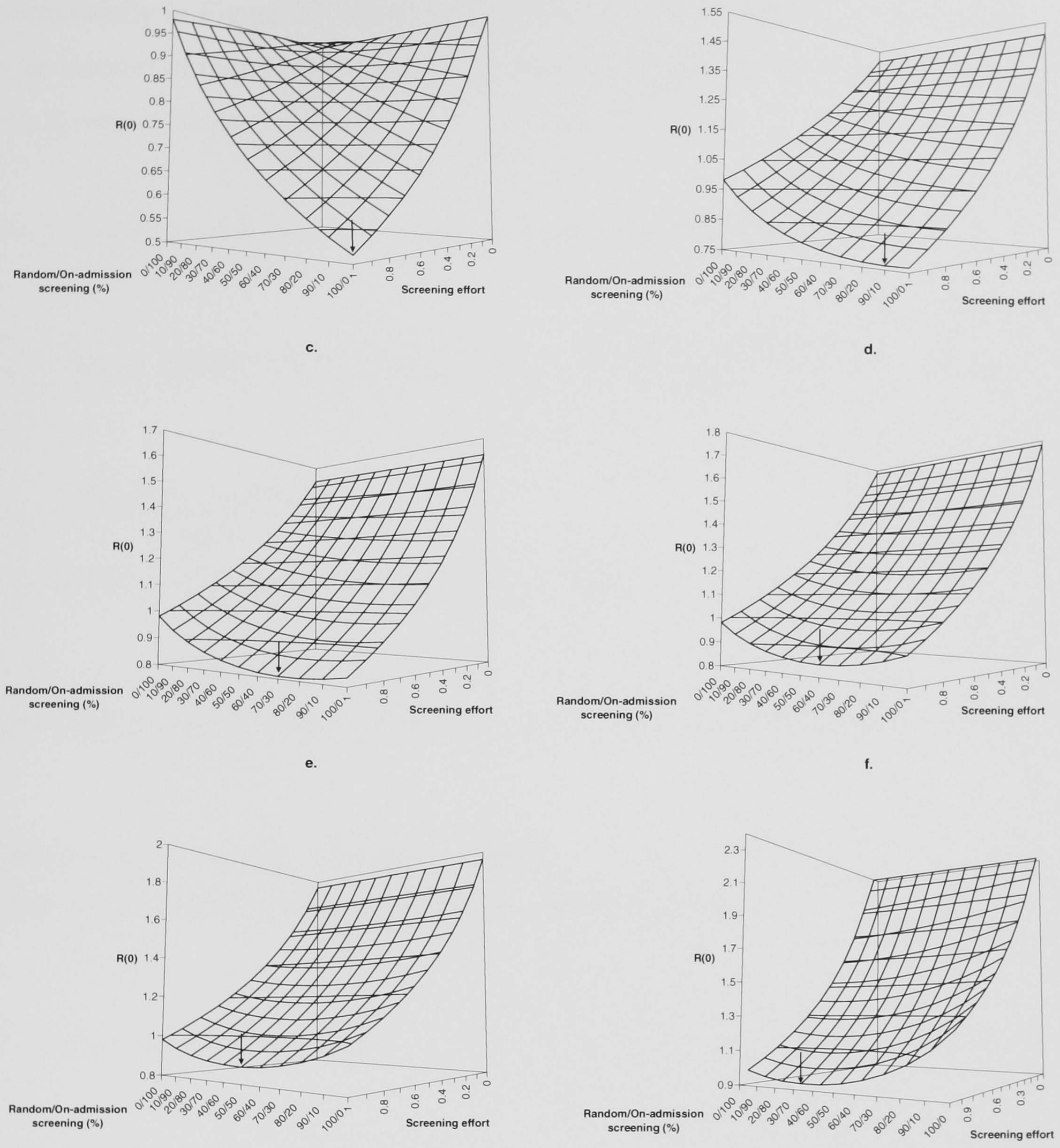



**Figure 2.3** Relationship between screening effort, screening strategy combination and $R_0$ under different initial P values. Initial conditions $R_0 = 1.01$, $r_0 = 0.98$, (a) P = 0.037, (b) P = 0.35, (c) P = 0.4, (d) P = 0.45, (e) P = 0.5, (f) P = 0.6. $\phi$ = range: 0-0.125, $\omega$ = range: 0-1 to create screening efforts from 0 to 1. The combination of screening strategies producing the lowest $R_0$, i.e. greatest control, is indicated by an arrow. Research for this figure was conducted with C.A. Scarff.

## 2.4 Deterministic model

A deterministic version of the framework described in section 2.2 and shown schematically in Figure 2.1 can be constructed by determining the rate of change in the number of individuals in each state using the events and their corresponding rates (given in Tables 2.1 and 2.2).

The resulting set of differential equations can be written as follows:

$$\dot{S}_H = \gamma UI_H + \gamma DNISO + \theta_1 S_{C1} + \theta_2 S_{C2} - \mu S_H - \frac{\beta S_H (UI_H + DNISO)}{NH} \tag{2.11}$$

$$\begin{aligned} \dot{UI}_H = {} & \frac{\beta S_H (UI_H + DNISO)}{NH} \\ & + (1-\omega)\theta_1 I_{C1} + (1-\omega)\theta_2 I_{C2} - \mu UI_H - \gamma UI_H - \phi UI_H \end{aligned} \tag{2.12}$$

$$\dot{ISO} = (\omega\theta_1 I_{C1} gISO) + (\omega\theta_2 I_{C2} gISO) + \phi I_H gISO - \mu ISO + fDNISO(\mu ISO) \tag{2.13}$$

$$\begin{aligned} \dot{DNISO} = {} & \phi I_H (1 - gISO) - \mu DNISO - \gamma DNISO \\ & + (\omega\theta_1 I_{C1}(1 - gISO)) + (\omega\theta_2 I_{C2}(1 - gISO)) - fDNISO(\mu ISO) \end{aligned} \tag{2.14}$$

$$\dot{S}_{C1} = \gamma I_{C1} + \mu S_H - \theta_1 S_{C1} - \delta S_{C1} \tag{2.15}$$

$$\dot{I}_{C1} = \mu UI_H + \mu ISO + \mu DNISO - \gamma I_{C1} - \delta I_{C1} - \theta_1 I_{C1} \tag{2.16}$$

$$\dot{S}_{C2} = \gamma I_{C2} + \delta S_{C1} - \theta_2 S_{C2} \tag{2.17}$$

$$\dot{I}_{C2} = \delta I_{C1} - \gamma I_{C2} - \theta_2 I_{C2} \tag{2.18}$$

### 2.4.1 Deterministic results

**No control**

In a situation where no screening occurs (Figure 2.4 (a)), the deterministic model shows the epidemic curve within the hospital reaching an equilibrium of approximately 400 infected individuals after approximately 2 years. The epidemic in the community population (b) is slower, with the build up of infected patients continuing in community group 2 once equilibrium has been reached in community group1. By the end of the study time (5 years) both community groups appear to have reached equilibrium with approximately 14,000 infected individuals in total.

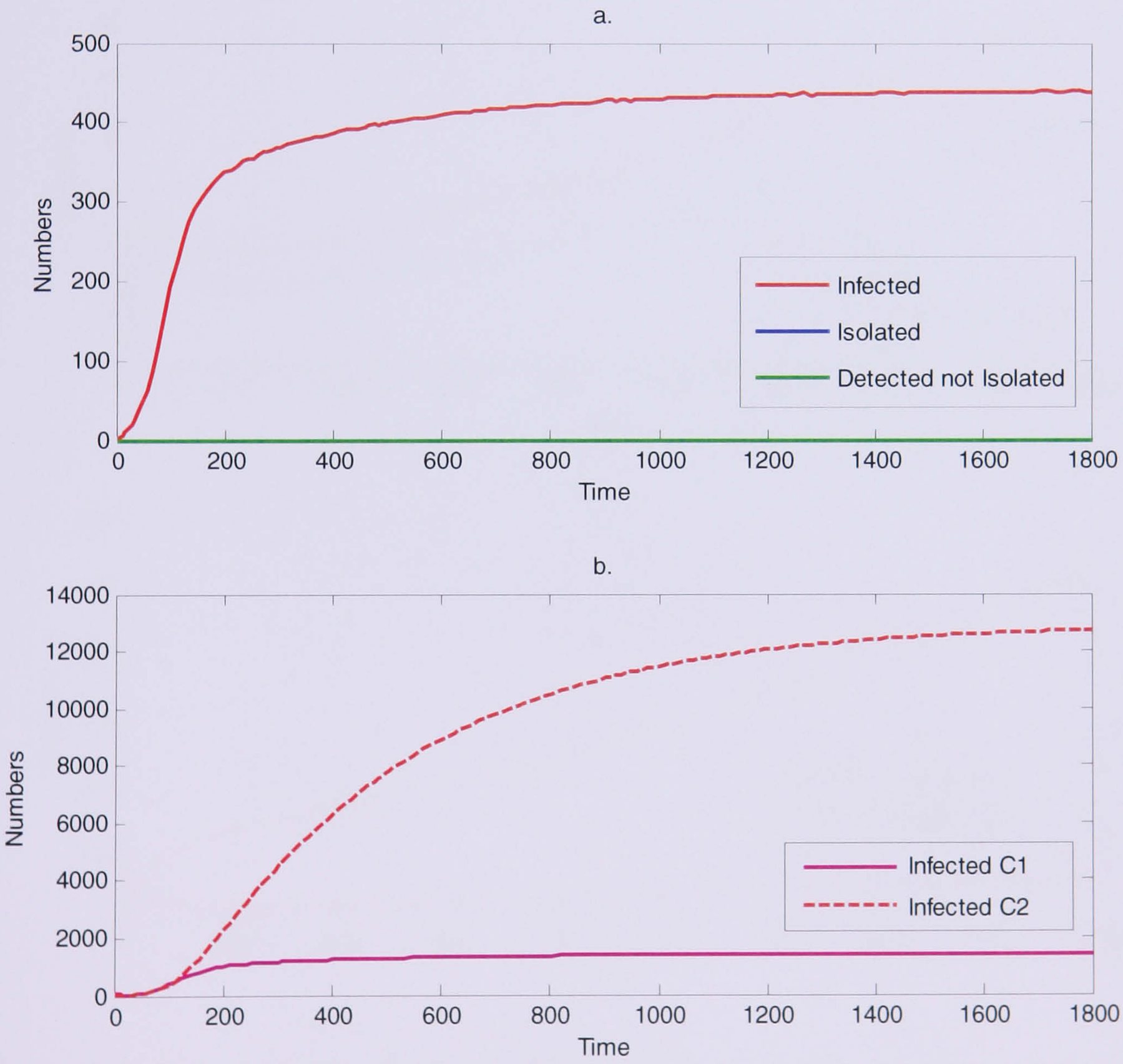



**Figure 2.4** Deterministic model results over a period of 1800 days (~5 years) when no control measures are imposed. Panel (a) shows the change in numbers in groups within the hospital population and panel (b) the change in numbers in the community population groups. Parameter values are set to those in Table 2.1.

## Comparing random and on-admission screening

On introduction of random screening (coupled with an isolation ward) as an infection control strategy (Figure 2.5) the numbers of infected patients in the hospital are reduced dramatically. Despite gradually increasing over the study period, numbers of infected patients within the hospital never exceed 15 (a) and the isolation ward capacity (20) is never breached meaning there are no detected but unisolated patients. This hospital control is reflected in the community (b) with far fewer numbers of infected individuals than in the situation without control (Figure 2.4 (b)). However, again numbers of infected individuals are steadily increasing throughout the study period.

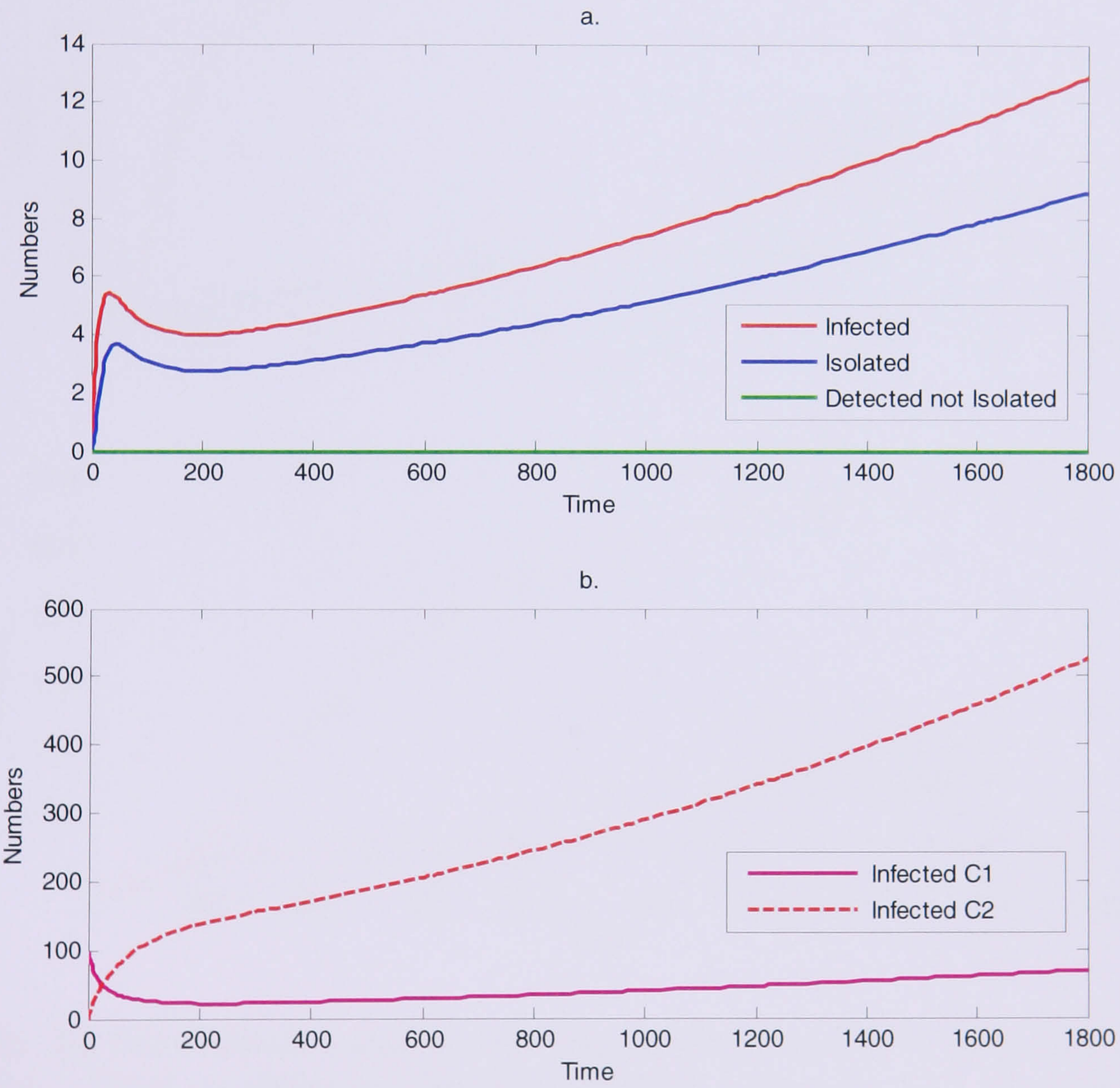



**Figure 2.5** Deterministic model results with a control strategy of random screening. Panel (a) shows the change in numbers in groups within the hospital population and panel (b) the change in numbers in the community population groups. $\phi$= 0.087 (corresponding to a screening effort of 70%), all other pparameter values are set to those in Table 2.1.

In contrast, the deterministic model results for a control strategy of isolation and on-admission screening display a dramatically reduced infection control capability. An epidemic is seen within the hospital (Figure 2.6 (a)) with the numbers of infected individuals reaching an equilibrium of approximately 300. Within a year the isolation ward reaches capacity and remains as such, resulting in a build up of detected but unisolated patients. The epidemic within the hospital is reflected in the community (b) with a build up of infected individuals occurring until equilibrium of approximately 13,000 infected individuals is reached.

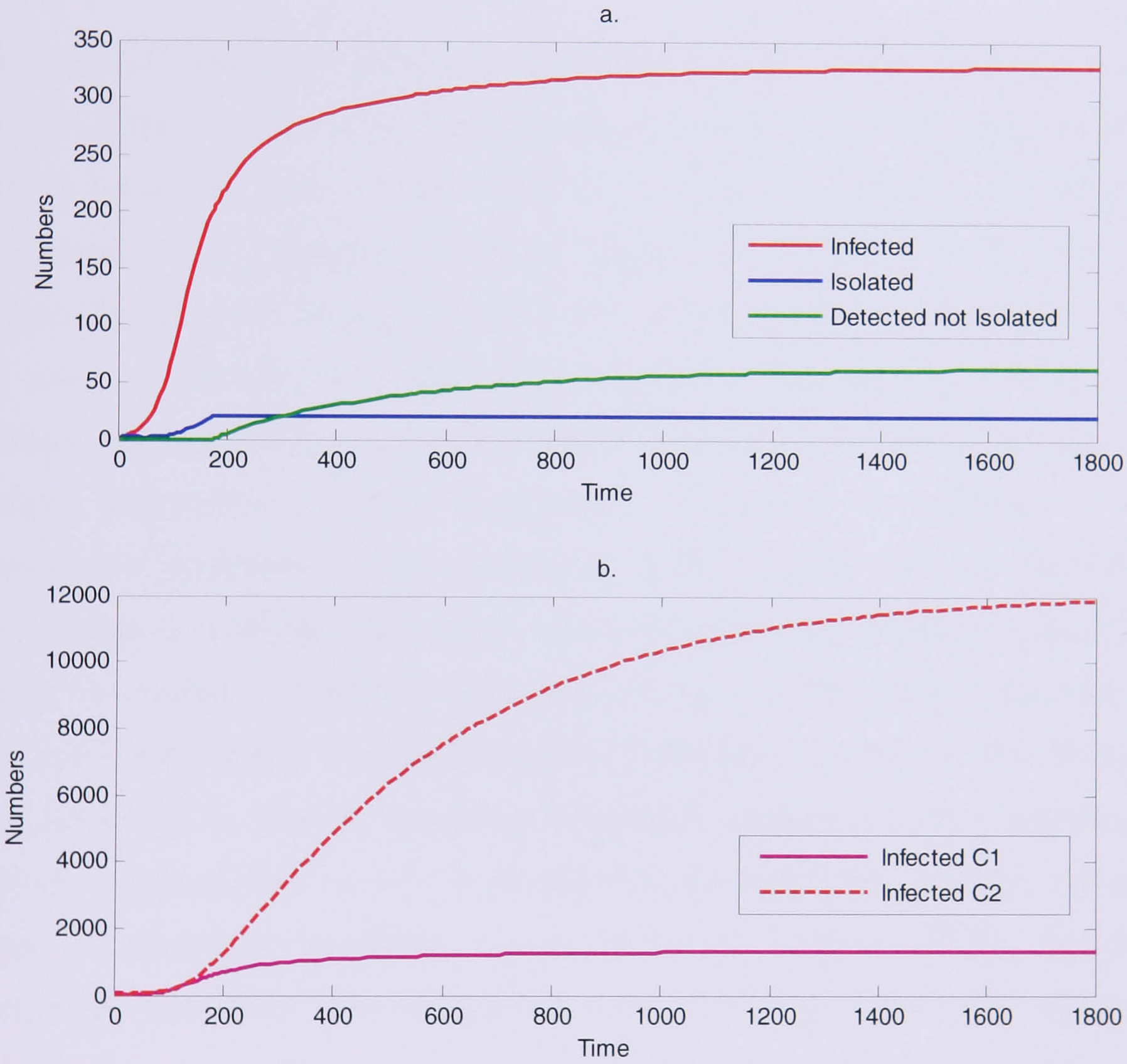



**Figure 2.6** Deterministic model results with a control strategy of screening on-admission Panel (a) shows the change in numbers in groups within the hospital population and panel (b) the change in numbers in the community population groups. $\omega = 0.7$ (such that 70% of the admissions/day are screened), all other parameter values are set to those in Table 2.1.

## 2.5 Discussion

Consideration of both the hospital and community population and movement between them within the model structure means that the transmission dynamics of HCAI are dependent on two factors: transmission from a single hospital stay and transmission due to readmission of infectious individuals. In this chapter these two factors were explored analytically in terms of reproduction numbers: the overall $R_0$ term being dependent on both transmission during a single hospital stay ($r_0$) and the probability of infectious readmissions (1/(1-P)).

An analytical exploration into the effect of an infection control strategy, in this case screening, on these transmission parameters showed that the reduction in $R_0$ brought about by each control strategy was due to influences on different components of $R_0$. Random screening within the hospital had the effect of reducing transmission from a single visit ($r_0$), whereas screening on admission had the effect of reducing the probability of infectious readmissions (1/(1-P)). As different screening strategies influenced different components of transmission, the relative importance of these components (dependent on setting) to the transmission dynamics strongly influenced which strategy was most beneficial. For example, in a setting where infectious readmissions are unlikely, transmission within the hospital (i.e. from a single hospital stay) has the greatest influence on transmission dynamics. It is therefore the strategy that can reduce $r_0$ that becomes most beneficial i.e. random screening. Whereas in settings of higher readmission rates the importance of 1/(1-P), to the transmission dynamics, increases and as a result on-admission screening, which works to reduce 1/(1-P), becomes increasingly beneficial. This relationship holds in settings of both $r_0>1$ and $r_0<1$. However, at $r_0>1$ only random screening can reduce $R_0$ to less than one, furthermore this can only be achieved at low rates of infectious readmission. When $r_0<1$ both strategies are able to reduce $R_0$ to less than one providing the level of effort put into screening is sufficiently high. A low $r_0$ (below one) also allows high rates of infectious readmission to be combated, but only at the highest screening effort levels (Figure 2.2 panel d). The investigations into combination screening tally with these findings in that with increasing readmission rates the

infection control strategy of greatest benefit includes an increasing proportion of on-admission screening.

These analytical results of the model framework could be compared to the results of a deterministic model of HCAI transmission. The deterministic results show epidemic behaviour in both hospital and community populations (for an $r_0$ of 1.27 and an $R_0$ of 1.32). Modelling the two screening strategies deterministically shows random screening to largely control infection within both the hospital and community, although prevalence gradually increases over the 5 year simulation period. On-admission screening, however, allows epidemic behaviour within the hospital, which in turn translates to an epidemic within the community population. These results agree with the analytical results for these particular parameter values, where P is low, $r_0$ is greater than one and screening effort is at 70%. Namely, in a setting of low P it is the reduction in $r_0$ that enables $R_0$ to be reduced to the greatest extent, therefore the greatest degree of control will be brought about by random screening. Only random screening can reduce $R_0$ to less than 1 for these particular parameter values (Figure 2.2 panel a).

From this chapter it has been shown that analytical and deterministic investigations into a proposed model structure/ framework can highlight factors with a potential to influence the transmission dynamics within the system, and therefore can provide some interesting hypothesis for further work.

# Chapter 3

# Using stochastic mathematical modelling as a theoretical test of control measures

## 3.1 Introduction

The efficacy of screening as an infection control strategy is assessed theoretically using the stochastic model described in Chapter 2. This is the first attempt to model both control (by isolation) and active surveillance in a single framework which considers both hospital and community populations. The majority of the research presented in this chapter has been published (Robotham *et al*, 2007a) and some presented at the 45th ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy), Washington, USA. Additionally, some of the work presented (where indicated in figure legends) was carried out with C. A. Scarff.

Firstly, surveillance and control of MRSA in an epidemic setting are investigated, through two screening strategies: random and on-admission. Comparisons of the two screening strategies in terms of numbers of detected infected individuals are presented. To examine the relationship between surveillance and control, the implementation of isolation once positive patients are identified is included, therefore determining how the effectiveness of *detection* for each strategy translates to the effectiveness of *control*. The combined effects of the amount of

effort put into each strategy (i.e. $\phi$ and $\omega$) and the capacity of the IW are considered. The outcome variables of interest are the apparent and real infection prevalences in the hospital and community (i.e. surveillance and control success). Additional to allowing targeted control, surveillance of infection (i.e. detection) plays an important role in measuring the magnitude of the problem, determining the penetrance of antibiotic resistance (e.g. vancomycin-resistant *S. aureus* (VRSA)) and determining the effectiveness of control. Consequently, control of infection by detection and isolation is not independent of surveillance. Here this interplay between surveillance and control is described.

## 3.2 Results

### 3.2.1 Surveillance of epidemic (no control)

Initially the effect of the two surveillance strategies in the absence of any control during an epidemic (i.e. from the introduction to endemic state) is considered. Figure 3.1 shows 10 epidemic simulations in terms of the real number of infections in the hospital and community (panels a and b respectively). With the chosen parameters the prevalence in the hospital and community reach approximately 400/1000 and 14000/170234 respectively. These values correspond well to those achieved using the deterministic model in chapter 2 (Figure 2.4).The apparent number in the hospital (i.e. those detected through active surveillance) is shown for the two screening strategies: random (c) and on-admission (d). There are two features to note. First, random screening is more efficient in that more infected individuals are detected (the equilibrium value is approximately 160 as opposed to approximately 80). Second, the pattern of timing of detection with random screening closely follows the pattern of the overall hospital prevalence, whereas detection with screening on admission follows the community prevalence pattern, which is slower with a pronounced lag of about half a year.

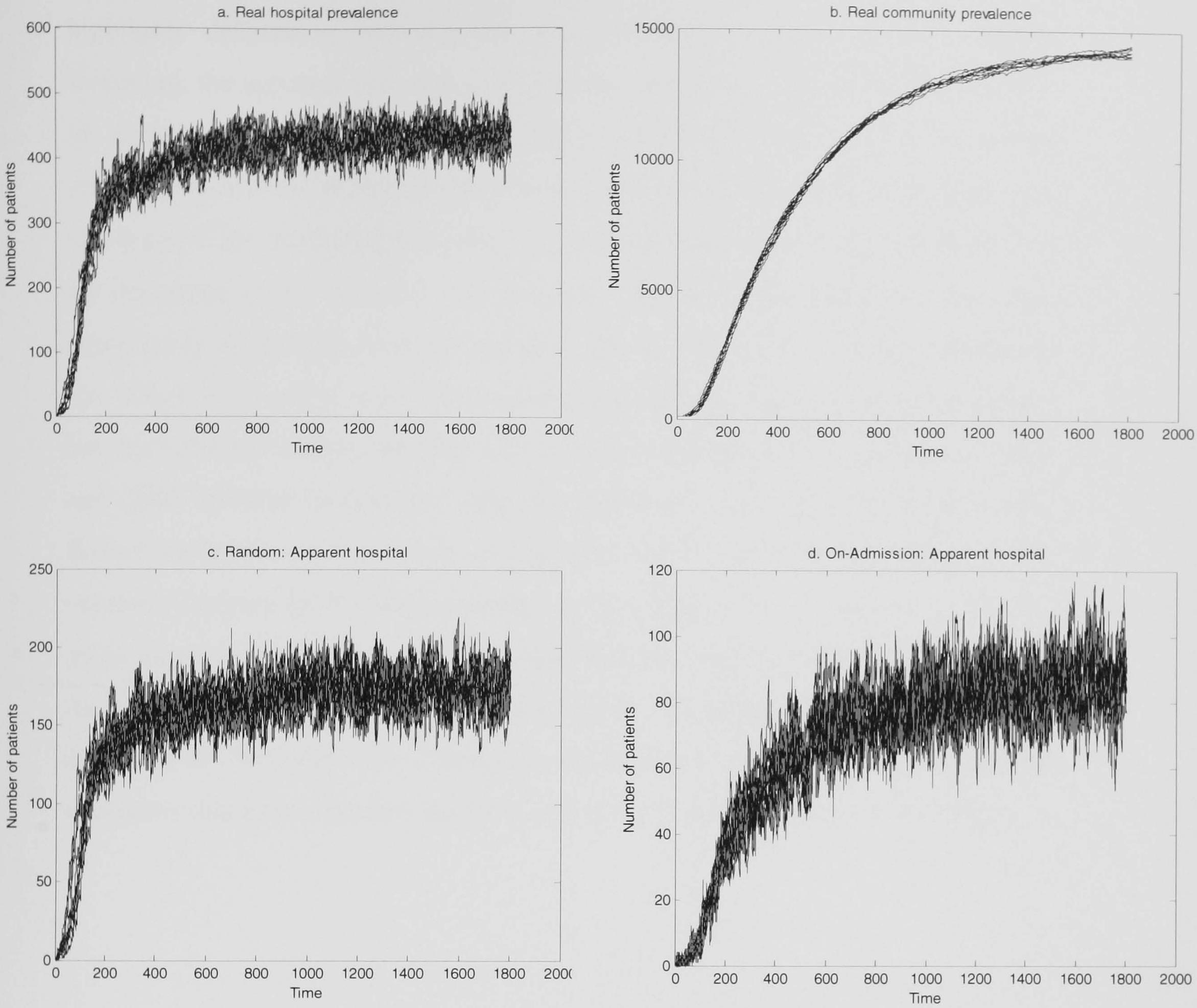



**Figure 3.1** Results of 10 simulations with no control over 1800 days (~5 years): (a) real hospital prevalence including both known and unknown infected individuals; (b) real community prevalence; (c) apparent hospital prevalence under random screening; and (d) apparent hospital prevalence under screening on-admission. Note the different vertical scales. Screening parameter values are $\phi$= 0.087 and $\omega$ = 0.7 (such that 70% of the admissions/day are screened). All other parameters are set to the values in Table 2.1.

The relationship between real and apparent prevalence for one epidemic further highlights differences between the two strategies (Figure 3.2). For random screening, the apparent prevalence reflects the real prevalence within the hospital, i.e. there is a linear relationship, so that a doubling in real hospital prevalence gives a proportional increase in the number detected (a). Surveillance efficiency is the slope of the relationship, so that, for example with $\phi$=1/8 days, about 50% of all infections in the hospital are detected (200 vs. 400). However, the same relationship is not seen between apparent and real prevalence in the community (b). There is an initial linear relationship between real and apparent prevalence, but once the real community prevalence reaches a threshold level (between 1000 and 2000 infected individuals), and the epidemic takes off in the community, further increases in community prevalence make very little difference to the numbers detected by random screening in the hospital. For example, for $\phi$=1/16 days, for all community prevalence values between approximately 2000 and 9000 the corresponding apparent prevalence results are within the narrow range of about 80 to 140. However, increasing the detection effort results in increased efficiency and more sensitive results (i.e. the relationship becomes more linear).

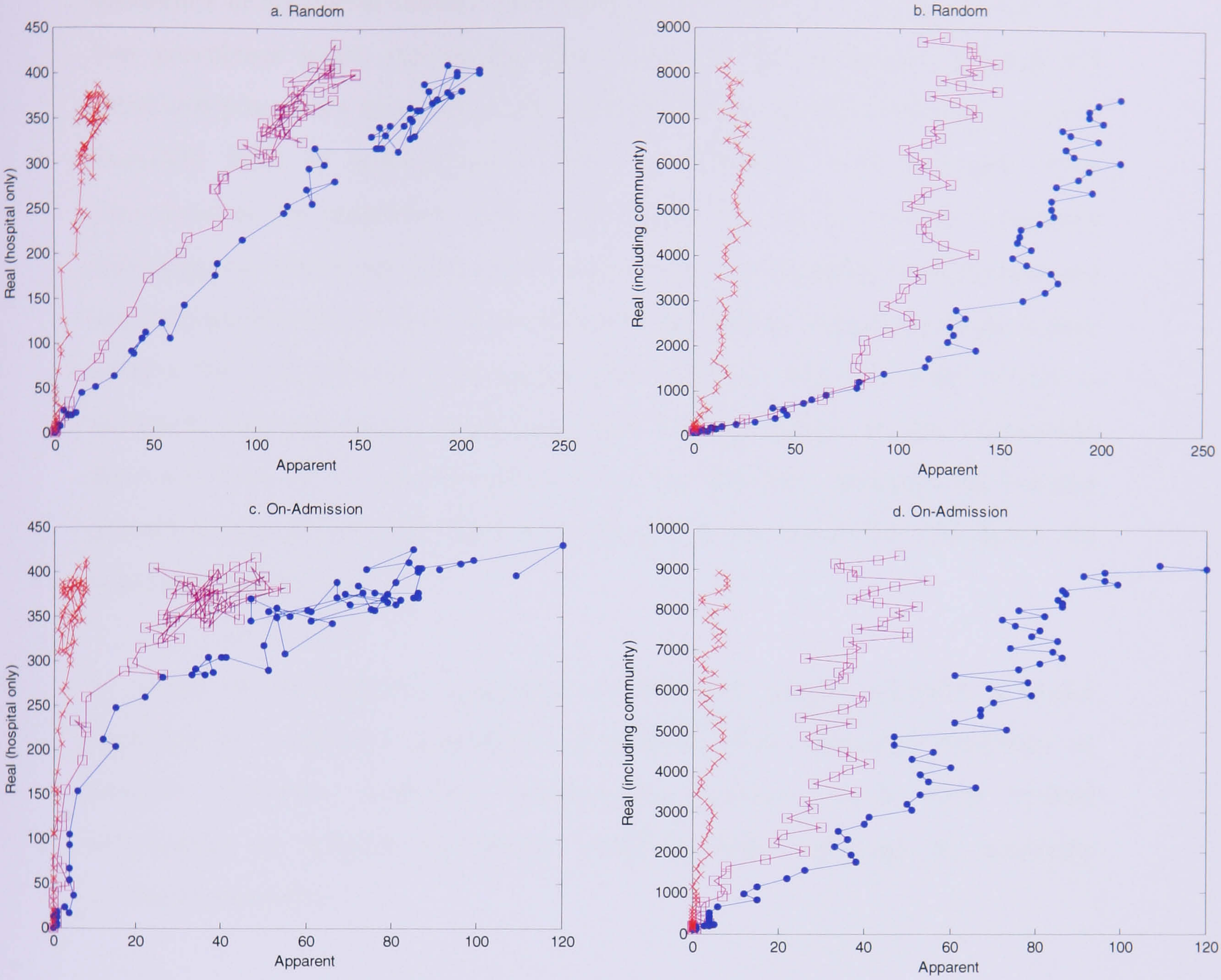



**Figure 3.2** Real and apparent prevalence for different surveillance effort levels over a single epidemic. Lines join adjacent points seven days apart during the epidemic, the total duration of observations = 1800 days (~5years). Graphs (a) and (b) display results for random screening with three values for $\phi$ : ● = 1/8 days, □ = 1/16 days, × = 1/133 days. Graphs (c) and (d) display results for screening on-admission for three corresponding values of $\omega$: ● = 1, □ = 0.6, × = 0.06. Parameters are set to the values in Table 2.1.

Screening on-admission provides less effective detection overall (note the difference in horizontal scales). This strategy underestimates hospital infection at low prevalence levels (during the early stages of the epidemic), although the relationship becomes more linear once infection levels become sufficiently high (a threshold level of approximately 250) (c), especially with increased effort (measured as the proportion screened on admission, ω). In contrast to random screening, on-admission screening reveals a linear relationship between real and apparent community prevalence meaning the apparent prevalence more accurately reflects the real prevalence throughout the epidemic. The efficiency of this is increased with increasing screening effort (i.e. the slope of the relationship decreases with an increase in effort). Note that for both strategies the hospital prevalence reaches an endemic state at the end of the simulation (the points are clustered together).

In terms of surveillance, screening on-admission clearly provides a better approach to estimating community prevalence than screening inpatients at random. However, screening on-admission provides much more limited information on hospital prevalence, which is better estimated by randomly screening inpatients.

### 3.2.2 Control of epidemic

Upon introduction of a control measure the values for $r_0$, P and $R_0$ are altered dependent on screening effort. The corrected $r_0$, P and $R_0$ values are 0.76, 0.037 and 0.79 for a random screening effort of $\phi = 0.087$ and 1.27, 0.011 and 1.28 for an on-admission screening effort of $\omega = 0.7$ (effort values correspond to those in Figure 3.1).

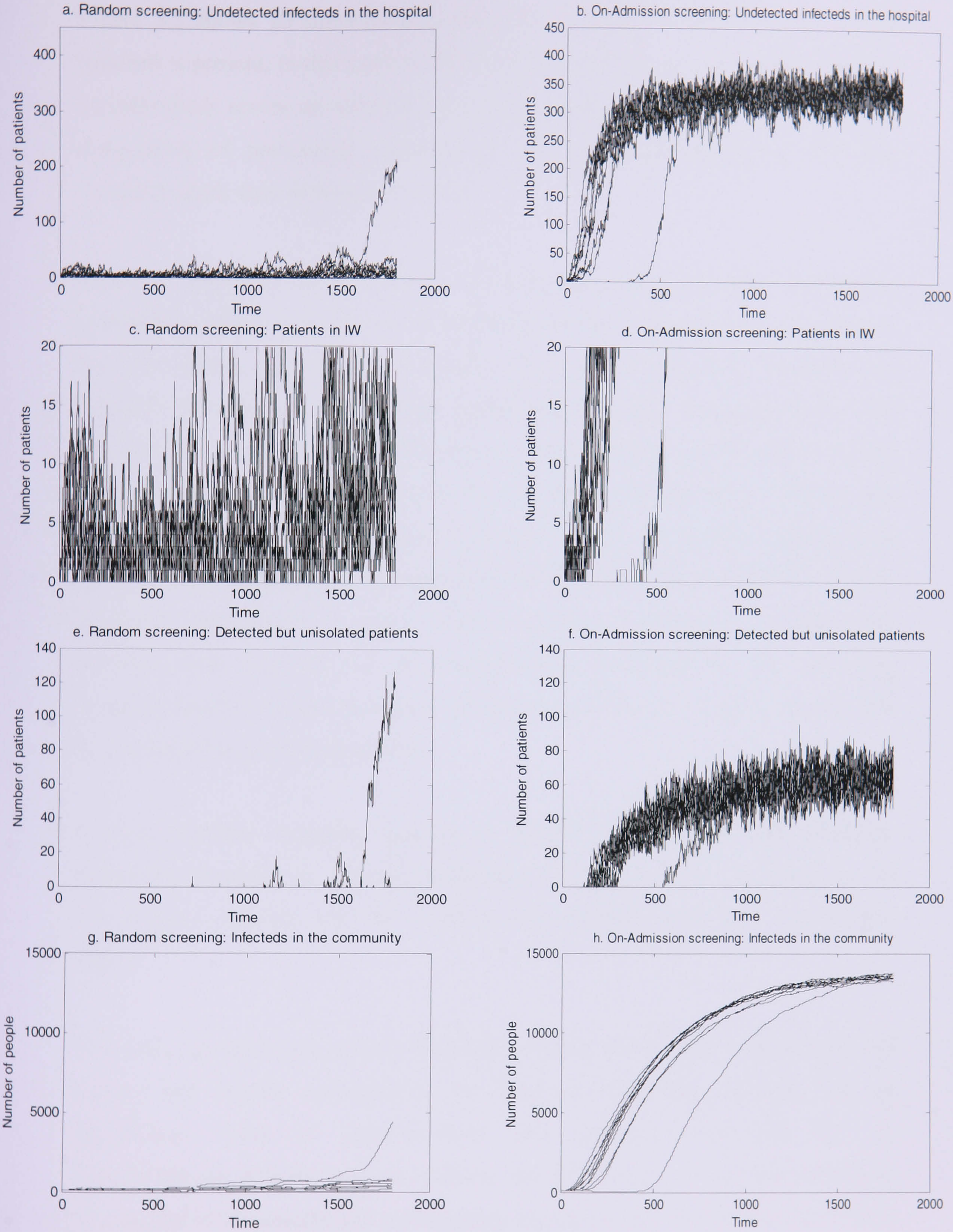



**Figure 3.3** Results of 10 simulations over 1800 days (~5 years) with an IW of capacity 20. Random screening ($\phi$= 0.087) is shown on the left hand graphs and on-admission screening ($\omega$ = 0.7) on the right. The four rows examine: hospital prevalence; number of patients in IW; number of DNISO patients and community prevalence. All other parameters are set to the values in Table 2.1.

Figure 3.3 shows 10 simulations under each screening strategy when a control measure is present, in this case an IW of 20 patient capacity, so that the detection of individuals serves an additional purpose: it allows them to be isolated, in the expectation of preventing transmission and, hence, an epidemic. The two strategies show very different dynamics.

Random screening gives greatest control; both hospital and community prevalence is lower than for on-admission screening (comparing a vs. b and g vs. h). The number of infected individuals in the hospital appears to increase very gradually throughout the simulation period under random screening. One of the simulations begins to show epidemic behaviour at the end of the period, but for most simulations the number of infected individuals remains below 50 with only small scale fluctuations. The capacity of the IW (20) is generally adequate with most detected individuals being able to be placed under control and IW overflow occurring infrequently (c and e). The community prevalence also gradually increases over time (g). For most simulations (excepting the one exhibiting epidemic behaviour) the maximum community prevalence is approximately 800 by the end of the simulation period.

Overall, random screening appears to exhibit control, but with gradually increasing numbers of infected individuals causing control capability to be increasingly stretched and IW overflow and epidemic behaviour increasingly likely.

Screening on-admission allows epidemics within the hospital which take off rapidly and remain uncontrolled; the endemic state that develops has an equilibrium value of approximately 300 infected individuals (b). In correspondence with the hospital epidemic the IW quickly reaches and remains at its capacity of 20 patients and subsequently overflows (d). The number of DNISO patients steadily increases up to an equilibrium value of approximately 60 (f). The community prevalence levels show a slower epidemic pattern than that in the hospital, reaching nearly 14000 infected individuals at equilibrium (h).

Overall, on-admission screening does not control MRSA under the chosen parameter values. The epidemics in all simulations take off quickly causing the IW to become overwhelmed, in turn leading to a build up of known positive patients who cannot be isolated.

Again, these stochastic results show very similar patterns to those achieved using the deterministic model in Chapter 2 (Figures 2.5 and 2.6).

### 3.2.3 Surveillance and control

Figure 3.4 explores the relationship between surveillance and control, looking at the effect of surveillance effort ($\phi$ and $\omega$) in terms of number of infections/detections summed over the simulation period (1800 days) given different control capabilities (i.e. different IW sizes).

Under random screening the average number of infections in the simulation period can be seen to decrease with increasing screening effort (a). The effect of increasing IW capacity is to reduce the level of effort required to achieve the same result e.g. to achieve a drop to 15000 infections per simulation period a detection effort of $\phi \approx 0.06$ is required when the IW capacity is 50, compared to a detection effort of $\phi \approx 0.09$ when the IW capacity is 10.

The results for screening on admission show a different picture (b); the average number of infections during the simulation period remains high until greater than 80% of admissions are successfully screened. Larger IW sizes correspond to slightly fewer infection events, but have relatively little effect i.e. the constraint is detection.

The number of detections over the simulation period for both policies is peaked with a single maximum. The initial increase is caused by the fact that as screening effort increases then so does the ability to detect infected individuals. However, the steady decline in numbers of detections that follows the peak is due to the fact

that the detection is enabling effective control. Therefore there are fewer individuals available to be detected, leading to fewer detection events. For random screening an increase in IW capacity causes the peak to be reached at lower effort levels and with lower numbers of detections, meaning that detection is efficient and isolation capacity is a constraint for control success.

For on-admission screening, the average number of detections over the simulation period (d) increases linearly with detection effort, up to an 80% screening effort. Detection effort values over this give a decreasing number of detection events, corresponding to the control seen after this effort level (b), i.e. once control occurs there are fewer infected individuals to detect. The peak in the number of detections occurs at a much higher effort level for on-admission screening (d) than for random screening (c), meaning that random screening is more efficient, i.e. less detection effort is required for successful control.

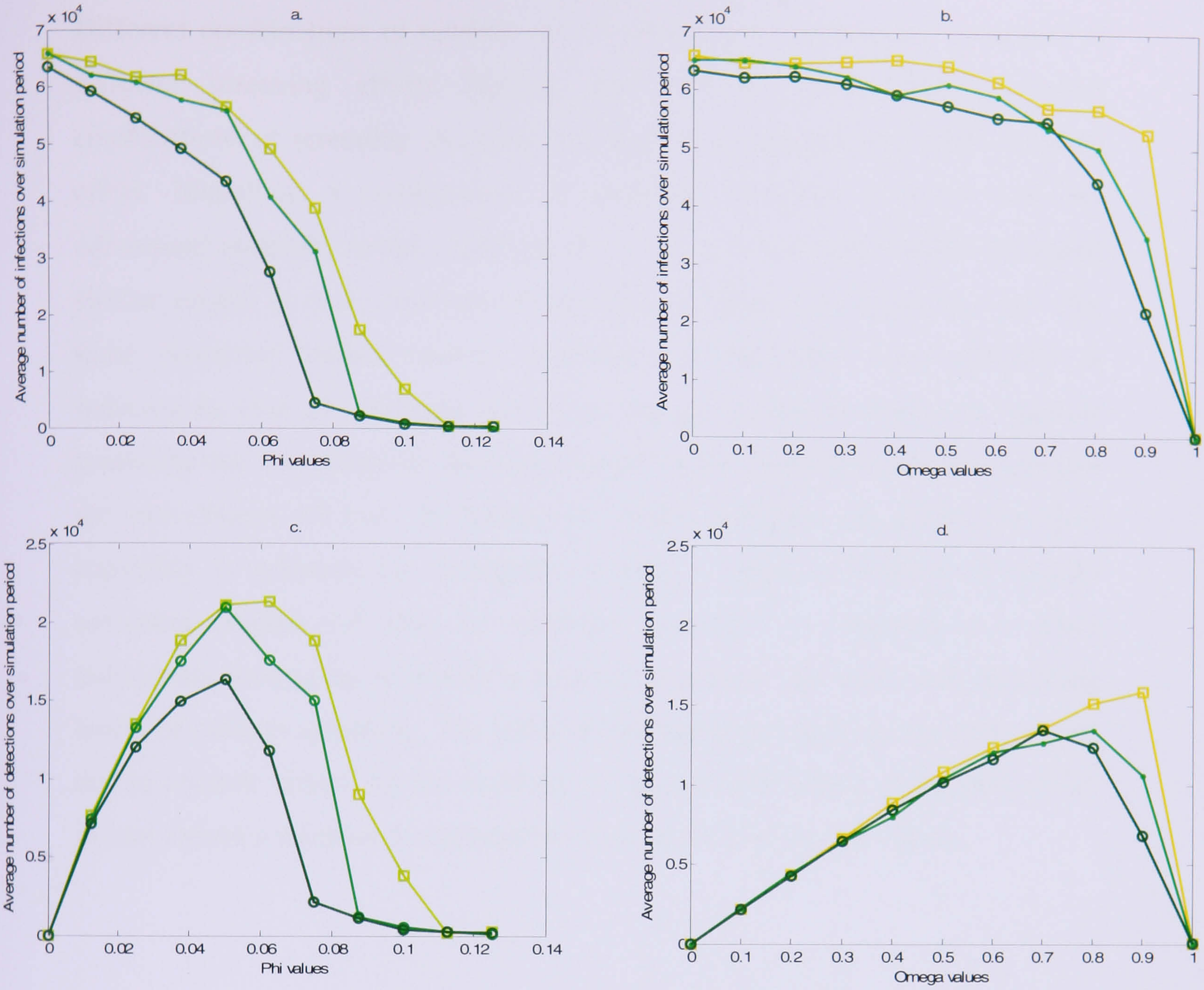



**Figure 3.4** Relationship between screening and control for random screening (panels a and c) and on-admission screening (b and d). Graphs show the average number of infection events (a and b) and detection events (c and d) over a simulation period (~5 years) from 10 simulations (note that the scale for (a) and (b) ranges from 0-65000 infections). The epidemics were run with different IW sizes: □ = 10, • = 20 and ○ = 50. All other parameters are set to the values in Table 2.1.

### 3.2.4 Combining random and on-admission screening

Different combinations of random and on-admission screening are compared at different screening efforts ranging from 0% to 100% where different combinations of screening strategies are applied to complete the total screening effort. Modelling a combination of screening strategies (random and on-admission) under the initial conditions $R_0 = 1.32$, $r_0 = 1.27$ and P=0.037 produced similar results to those deduced analytically in Chapter 2 (Figure 2.3 (a)). For these parameter values random screening is consistently more effective at reducing $R_0$ over all screening efforts and the greater the proportion of random screening that contributes to the screening effort the fewer transmission episodes are seen (Figure 3.5 (a)). Reflecting the results in Figure 3.4, greater detection capability is achieved by strategies including a larger proportion of random screening (Figure 3.5 (b)). In addition, less effort is required (i.e. fewer individuals need to be screened) to achieve maximum detection with increasing levels of random screening. The decrease in detection following the peak occurs due to control; control causes numbers of infected individuals to decrease which in turn causes a decrease in the number of detected infected individuals.

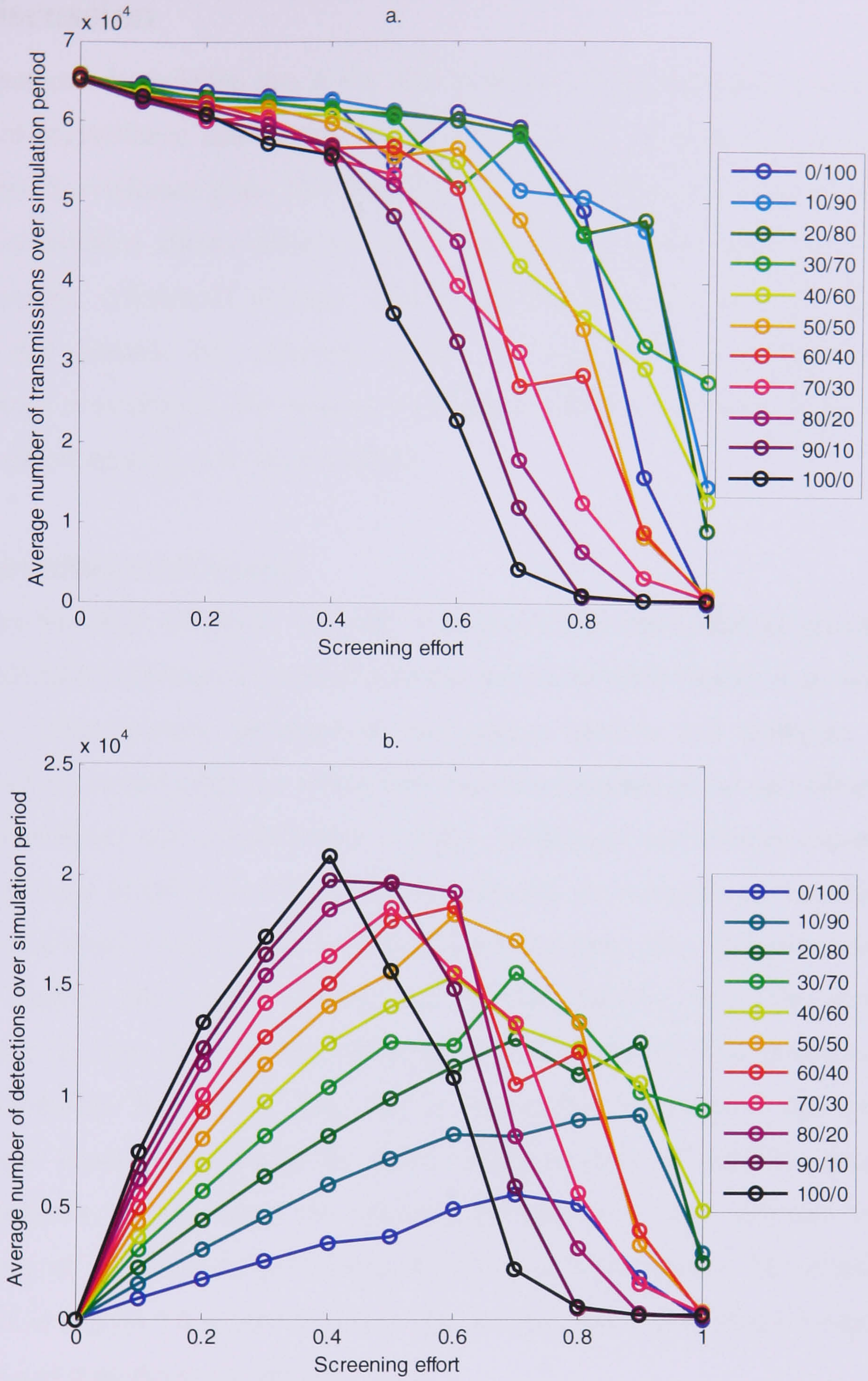



**Figure 3.5** Relationship between screening effort and control for different combinatory screening strategies. The average number of transmission events (a) and detection events (b) over a simulation period of 1800 days for 10 simulations is shown. Where $R_0$ = 1.32, $r_0$ = 1.27 and P=0.037. Different lines represent percentages of random / on-admission screening forming the screening effort; values are given in the legend. The program code for this figure was written with C.A. Scarff.

## 3.3 Discussion

To the author's knowledge this is the first attempt to simultaneously consider the effects of surveillance and control on the transmission dynamics of nosocomial infections. Surveillance plays two important roles with respect to control. Firstly, active surveillance allows detection of infected (and possibly more importantly asymptomatic, colonized) patients. This identification is necessary for targeted control that curtails the infectious period ("isolation"). The second role of surveillance is to estimate the burden of infection, which is essential if the success of any control strategy is to be quantified.

### 3.3.1 Surveillance and control

For many bacterial infections, the risk of disease (with overt clinical symptoms) given infection/colonization is small and dependent on other factors (e.g. surgical wounds, catheterisation, presence of intravenous devices and antibiotic use). Consequently, monitoring and controlling infection requires active surveillance to detect individuals with asymptomatic carriage. Inadequate surveillance causes any control strategy to fail as too few infectious patients are isolated and transmission is not sufficiently reduced (i.e. $R_0$ remains greater than one). However, despite actually failing, the control strategy can appear effective since the apparent prevalence is low due to the inefficiency of detection. The potential for misinterpretation lies in the fact that a successful surveillance and control programme would give exactly the same results in terms of numbers detected. When infection is controlled the apparent prevalence is low, not due to the inadequacy of surveillance, but because it reflects real prevalence. This finding is displayed in Figure 3.4 (c and d) where the same apparent prevalence is seen for both low and high detection efforts.

Such a phenomenon is outlined in a study by Tomic *et al.* (2004) where, upon introduction of aggressive infection control measures, incidence was seen to increase despite the proportion of MRSA cases acquired decreasing (i.e. because of the enhanced screening, cases that would previously have remained undetected were being elucidated).

The two screening strategies examined here display different control capabilities in an epidemic situation simply due to the differences in detection capability. With random screening, the apparent hospital prevalence reflects the real hospital prevalence consistently for all real prevalence values, i.e. there is a linear relationship (Figure 3.2 panel a). Therefore epidemics can be prevented (by isolation) while infected numbers are still low. The IW can cope with these small numbers of detected patients and the epidemic can be controlled before it becomes endemic. By contrast, screening on admission means that apparent prevalence reflects community prevalence accurately, but reflects real hospital prevalence only when real prevalence levels are high (i.e. when the hospital prevalence also reflects community prevalence) (Figure 3.2, bottom row). Therefore the IW is more likely to be overwhelmed and the control strategy fail (Cooper *et al.*, 2004a).

At the start of an epidemic, the majority of infections are amongst inpatients, so provided there is isolation capacity, epidemics within the hospital are controlled by random screening before they disseminate into the community (Figure 3.3 (g)). Whereas, screening on admission cannot detect infected individuals in the hospital, who may be either a) readmissions of infected individuals from the community (the probability of which increases as the community prevalence increases) that remain unscreened (with a probability of 1-ω) or b) those who have acquired MRSA whilst in hospital. Therefore these patients provide an unchecked source of infection. Additionally, DNISO patients are also a potential source of infection. With on-admission screening, the number of DNISO patients resembles the epidemic pattern seen in the community because IW overflow is caused only by admitted patients (i.e. from the community). As soon as the IW becomes full it remains full, therefore all admitted, screened patients move straight into the DNISO class. Consequently, whatever the levels of infection look like in the community, this pattern will be reflected in the hospital.

Control of dissemination of MRSA throughout the community requires effective control of nosocomial MRSA transmission (Salgado *et al.*, 2003) and therefore

the surveillance/control strategy adopted, whilst not neglecting community effects, should concentrate on reducing hospital transmission. This implies that on-admission screening alone cannot be used to control MRSA epidemics or any other infection which is driven by transmission between inpatients. This would apply to the pending epidemics of VRSA. However, on-admission screening may play an important role in surveillance and control of endemic infection (i.e. when it is well established in the community); in particular it provides an estimate of the infectious assault a hospital is experiencing, community prevalence and past transmission.

There is an apparent contradiction in that Figure 2.2 (a) shows that for on-admission screening the overall $R_0$ can never be brought below the within-hospital $r_0$, meaning that using these parameter values, with an $r_0$ greater than one ($r_0$ = 1.27), on-admission screening will never be able to control hospital infection once it is established even at 100% screening (i.e. $\omega = 1$). However, in Figure 3.4 on-admission screening at $\omega = 1$ allows control. This is due to the assumption that at $\omega = 1$ 100% of admitted patients are screened and all of these screens effective. As all infected individuals are assumed to be in the community population initially, 100% effective screening will prevent any infectious individuals ever entering the hospital i.e. the screening barrier is never breached. Therefore, despite the within-hospital $r_0$ being greater than one no infectious individuals are ever actually present within the hospital to transmit MRSA.

From these stochastic results, it has been shown that screening inpatients randomly provides the best information on hospital prevalence (Figure 3.2) and is most effective at reducing the rate of infection within the hospital (Figure 3.4). In contrast, screening on-admission provides a better approach to estimating community prevalence (Figure 3.2), but does not reduce within-hospital $r_0$; therefore the overall $R_0$ can only ever be reduced to the initial within hospital $r_0$ value (Figure 2.2 (a)). As transmission is determined by the within-hospital reproduction number, random screening becomes the more effective strategy overall. Therefore the stochastic results in this section agree with both the

analytical results and deterministic model results deduced in Chapter 2 for these particular parameter values, in that random screening is more effective at epidemic control.

### 3.3.2 Consideration of setting: the effect of reproductive number and readmission rate

The finding that random within-hospital screening does more to control MRSA than on-admission screening may seem counter intuitive. However, it can be explained by consideration of the degree of patient movement around the system i.e. the frequency of readmission.

As previously described, in terms of basic reproduction numbers, addition of random screening (at rate $\phi$) changes the within-hospital $r_0$ to:

$$r_0' = \frac{\beta}{\mu + \gamma + \phi}, \tag{2.9}$$

whereas, on-admission screening (with proportion $\omega$) has the effect of reducing P to:

$$P' = (1 - \omega)P\,. \tag{2.10}$$

In other words, random screening reduces transmission within the hospital arising from a single visit, whereas on-admission screening reduces transmission which considers movement between the hospital and community by reducing the probability of multiple infected returns to hospital. Therefore, admission screening may become increasingly effective when either a) multiple returns to hospital become more likely, or b) multiple returns are more likely to be infected i.e. there are higher infection levels within the community. As the simulation results presented use a particularly low readmission rate (P=0.037) i.e. where multiple returns to hospital are unlikely, admission screening is less likely to be effective.

### 3.3.3 Combining random and on-admission screening

It seems intuitive that a combination of screening strategies would be desirable, in that both hospital transmission and infectious assault could be reduced. Further research is required to determine optimal combination strategies, within given constraints (e.g. the number of patients that can be screened per day), and dependent on given goals. The community prevalence and pathogen transmissibility values will help determine the optimal combination, i.e. the optima will change for different epidemic/endemic situations. For example, if community prevalence is high and transmissibility low then a reduction in $R_0$ through screening on-admission may be most effective, but in a setting of low community prevalence and high pathogen transmissibility then a reduction in within-hospital $r_0$ would likely be most beneficial and so random screening favoured.

The stochastic results for different combinations of random and on-admission screening for specific $r_0$ and P values (Figure 3.5) agreed with the analytical results (Figure 2.3 (a)). Transmissions decreased with increasing screening effort due to control. Detections increase before control is achieved and subsequently decrease upon control because there are fewer infected individuals to detect. An increase in control corresponded with an increase in the proportion of random screening. Comparing the stochastic results to the analytical descriptions of the behaviour of $R_0$ for the corresponding parameter values (Figure 2.2 (a)) shows similar trends. The analytical results show the greatest reduction in $R_0$ to be achieved by random screening (due to the reduction in $r_0$) and that $R_0$ is brought below 1 for all screening effort levels above 0.35. The stochastic simulations (Figure 3.5) also show random screening to bring the greatest level of control. This control corresponds to the greater surveillance capability of random screening, where a greater proportion of the infected population can be detected with lower effort levels.

### 3.3.4 Targeted screening

Screening through routine clinical specimens has been shown to be inadequate and an active screening programme will generally be required to control MRSA (Coello *et al.*, 1994). The random and on-admission strategies included here are expensive and intensive. In reality screening is likely to occur in a more targeted way, in that certain criteria help determine which individuals are to be screened. For example, van Saene *et al.* (2004) suggest only those at high risk should be targeted and less effort given to those where MRSA is unlikely to increase mortality. Targeted screening to high risk groups alone has been shown effective in a number of studies (Girou *et al.*, 1998; Girou *et al.*, 2000). Wernitz *et al.* (2005) find on-admission screening of defined risk groups for MRSA carriage, combined with preventive isolation at admission, may be able to prevent HA-MRSA infections in an endemic setting. The risk groups were defined as either: patients with a known history of MRSA colonization or infection; patients transferred from foreign hospitals or hospitals where MRSA was endemic; or patients with at least two other high-risk characteristics such as residing in a nursing home, requiring dialysis or having an invasive device. Other targeted approaches include screening HCW to prevent subsequent transmission to patients (Blok *et al.*, 2003), and also so called 'ring-fencing' where screening is targeted to the contacts of a known case (Drinka *et al*, 2004).

A potential problem with these targeted methods is that their failure may go unnoticed due to the fact that those individuals who are not specifically targeted may provide a reservoir of undetected infection. As no screening would occur to untargeted individuals, no MRSA would ever be detected; however this would not necessarily mean that MRSA was not present i.e. there may be large differences between real and apparent prevalence. Thus targeted methods of screening, unless implemented carefully, may lead to control failure. Randomly screening outside the target group may be a way of overcoming this problem. This is supported by the previously described result from Figure 2.3, in that despite the efficacy of on-admission screening increasing with P, even at the highest P values 100% on-

admission screening is sub-optimal, with some degree of random screening always being required.

### 3.3.5 Limitations of the model

The main limitations are due to the simplification of the system and resulting reduction in heterogeneity.

As homogeneity is assumed no patient is more or less likely to transmit or contract MRSA than any other. Heterogeneity in patient susceptibility (to infection and disease) and infectivity is also missing. It is therefore assumed that the chance of a susceptible contracting the infection is equal on every contact with an infected patient and this is not the case. The chance of an infected or colonized person passing the infection on depends on the amount of bacteria they shed and where their infection or colonization is localised to. Heavy dispersers are often infected individuals who have widespread eczema or large burns, but patients with upper respiratory tract infections or colonized individuals may also be dispersers (Ayliffe *et al.* 1998; Sherertz *et al.*, 1996).

Screening of patients is said to result in 100% detection within the model. Realistically no screening method is 100% efficient and incorrect screening results could drastically affect the course of infection. There is also assumed to be no delay between screening an individual and receiving the results. In reality it can be several days until the results of any screening test are received, and in this time if the patient is not isolated and they are infected they are free to transmit to others. Furthermore, a colonized patient may be even harder to detect than those who are infected (Ayliffe *et al.*, 1998). Additionally, the assumption that the rate of discharge is equal for all hospital sub-groups ignores a particular feature of MRSA: it increases length of stay. Perhaps most importantly, heterogeneity in patient contact rates is not included, other than to assume that recently discharged patients have a higher rate of readmission. For example, the possibility that prolonged length of stay and/or infection with MRSA (as well as other factors such as age) might increase the readmission rate is not included. It is likely that

the "mixing" of patients and staff will have important impacts on the transmission dynamics, especially when considering multiple healthcare facilities with a single community reservoir. Movements of individuals (particularly persistent carriers) between hospitals, long-term care facilities and community populations need to be included in order to model MRSA transmission dynamics effectively (Smith *et al.*, 2004; Smith *et al.*, 2005).

It must be kept in mind that this model is not meant to be used as a forecasting tool, but instead to give an indication of factors that would contribute to a successful control strategy. The model forces a theoretical framework to be established therefore making assumptions a necessity, which in turn helps identify areas in which more information is needed (Austin and Anderson, 1999a).

### 3.3.6 Summary

Surveillance is essential to infection control and the particular surveillance strategy adopted can dramatically alter the effectiveness of this control. Given exactly the same control strategy and setting, one surveillance strategy may allow a particular control method to work and prevent spread, whilst another may cause it to fail and an epidemic to ensue. Moreover, effectiveness of surveillance can not only influence control success, but also the quantification of this success; effective surveillance and control exhibiting prevalences that mimic those when there is no control and ineffectual surveillance.

From mathematical simulations, screening randomly within the hospital was found to be an effective strategy for hospital surveillance and screening on admission to be effective at community surveillance. Additionally it was found nosocomial control, brought about by effective hospital surveillance, also prevented epidemic behaviour in the community. Thus making random screening the more effective strategy overall for the parameter values chosen.

Analytical results showed the optimal screening strategy to be highly dependent on the readmission rate of infectious patients, in that when readmission rates were

low control within the hospital was most beneficial compared to prevention of infectious admissions from the community being the priority when readmission rates were high. The results highlight that the consideration of setting i.e. the characteristics of the infectious agent (e.g. reproductive value), the characteristics of the host population (e.g. the degree of mixing between sub-populations), is essential in the development of a successful infection control strategy.

# Chapter 4

# Hospital and patient demographics at the University Hospitals of Leicester NHS Trust

Despite the existence of a wealth of data on patients admitted to UK hospitals there is seemingly little published about the demographics of the patient population within hospitals. Hospital admissions data provide an excellent resource for generating an overview of patient demographics; information on which would be invaluable for many areas of epidemiology and infection control.

The objective of this chapter is to describe such demographics. This was carried out though various analyses of hospital admissions data, from the three hospitals comprising the University Hospitals of Leicester (UHL) NHS Trust, over the period 1 April 1998 to 31 March 2005. A description of the study setting will be presented and following this basic summary statistics and frequency distributions as well as investigations into the association between a number of factors such as age, gender, hospital, ward type/specialty with hospital visit patterns including length of stay in hospital.

## 4.1 Introduction

Hospitals collect and retain a wealth of information on each of their patients. Data on patient demographics such as age, sex and medical history exist in the form of medical records and in an array of computerised systems. This information is commonly used for research studies investigating specific diseases or syndromes, often attempting to assign risk factors and relate patient demographics to prognoses or surgery outcomes (Bergeron *et al.*, 2005; Carbonell *et al.*, 2005a; Carbonell *et al.*, 2005b). Another application is in analyses of resource usage and economics using Hospital Episode Statistics (HES). However, these data could also be used more generally to give an overall picture of patient demographics.

The patient population within a healthcare institution is determined by the interaction of the basic processes of immigration (admission) and emigration (discharge or death). Patients are admitted from the community which contains a population with different histories of admission. An understanding of the demography of the patient population is important from a healthcare management viewpoint in that flow through the healthcare system is a key component of resource use and functionality (Marshall *et al.*, 2005). Of particular interest here is the infection dynamics of HCAI: in terms of infection control it is the patient population dynamics that define the context within which infection is acquired and transmitted. Information about the hospital population and changes to it could potentially provide insights into factors connected with infection rates and trends. An exploration of patient flow including readmission patterns would be particularly useful as it may translate to readmission of a particular pathogen into the hospital environment. If carriage of the pathogen persists over long time periods the number of transmission events caused by each case may be distributed over several hospital admissions making reintroduction from the community an important factor in transmission (Cooper *et al.*, 2004a).

However, despite the potential benefits of such information, to date there have been few studies into, or descriptions of, basic hospital demographics, especially over long time periods. This may be due to the fact that such extensive, detailed

and up-to date data are required which can be difficult to obtain, will be different for every hospital and will change over time. This chapter presents patient demographics for the UHL NHS Trust using patient admissions data collected from the three Leicester hospitals in the time period from April 1998 to April 2005.

The first section focuses on the demographics of the admitted population; the second section examines the length of stay of each of these admittees in terms of their demographic group. Following this, the demographics of the patient population within hospital are established. Within this framework a number of factors are investigated, such as age, sex, hospital and ward type/specialty. These investigations are extended in Chapter 5 where patterns of patient movements within the Trust are explored.

## 4.2 Methods

### 4.2.1 The dataset

The dataset used for these analyses comprised unique patient admissions into the UHL NHS Trust from 17th April 1994 though to 31st March 2005. The Trust comprises 3 hospitals: Leicester Royal Infirmary, Leicester General Hospital and Glenfield General Hospital, which collectively have a catchment area of approximately 1 million people across the city of Leicester, and the counties of Leicestershire and Rutland.

The source of the data is the hospital's principal administration system (Hospital Information Support System (HISS)). The system records all manner of demographic information; including age, date of birth, sex, ethnicity, and address. Additional data such as admission/discharge dates, admitting hospital site and ward, specialty etc are also recorded by a number of groups of staff such as Ward Clerks, Clinical Coders and Clinic Coordinators from a variety of sources such as patient's case notes. The HISS enables reporting and analysis that facilitates the management of performance, commissioning, clinical indicators and other operational targets for the Trust.

Key outputs of the data warehouse are:

- Internal (UHL) clinical and performance monitoring reports
- Mandatory returns to the Department of Health
- Commissioning datasets which are sent to the Secondary Users Service and are the source of commissioning, Payment by Results and HES data which all contribute to how UHL is measured and generate income for activity performed

Variables included in the dataset used for these analyses were unique patient identifier (i.e. the identification of patients on successive admissions was possible), sex, unique hospital stay identifier, hospital stay duration (nights),

admitting hospital, discharge hospital, age at admission (years), admission date, discharge date and discharge specialty name. Both inpatients and outpatients were included within the dataset and were labeled accordingly making discrimination between them possible.

### 4.2.2 Data cleansing

Using SPSS (Version 14.0 for Windows) simple exploratory analyses of each variable were carried out, revealing inconsistencies and anomalies. It was found that the data collected before 1998 was incomplete. Therefore it was decided to include data from 1st April 1998 through to 31st March 2005 only. Missing data within this time period was infrequent, but where it did it occur it was decided that any case with missing data should be excluded from any analysis using that particular case. The only other discrepancy found was with the variable 'age at admission' in which negative numbers had been entered as the patient's age. In only 30 cases (out of n = 1401471) did this occur, therefore due to the small numbers involved it seemed reasonable to exclude these cases from any age related analyses without compromising the results.

### 4.2.3 Data analyses

**Section A: Admissions**

Frequency distributions of admissions to the Trust based on age, gender, specialty and hospital were determined using a combination of SPSS (Version 14.0 for Windows) and Microsoft Office Excel (2003). In addition to Trust level investigations trends were also investigated at the individual hospital level, again with respect to age, specialty and gender. For some analyses results using all admissions (inpatients and outpatients) are compared to admissions of inpatients (n=1401471 and n=679588 respectively), where the trend for inpatients alone resembled that of all patients, the results for all patients are presented.

**Section B: Length of Stay**

Analyses of length of stay in hospital by age, gender, specialty and hospital were carried out, again using a combination of SPSS and Excel. Results are presented in terms of all admissions and also in terms of inpatient admissions only.

**Section C: The Patient Population**

The results from Sections A and B, i.e. who is going into hospital and who is staying there, allow information about the patient population to be determined. Distributions describing who is in hospital over time by age and gender are determined for the Trust as a whole and also for each hospital individually. For these analyses the patient population was determined for one particular month (March) over three consecutive years. The years 2001, 2002 and 2003 (i.e. those in the middle of the dataset) were chosen to reduce the problems associated with censoring.

## 4.3 Results

### 4.3.1 Section A: Admissions

**Trust Level**

Admissions to the Trust, by both inpatients and outpatients collectively, ranged from 14732 to 19442 per month and increased gradually over the 7 year period. Excluding outpatients, these figures drop to 6824 and 9177 respectively, but remained more constant over the study period (Figure 4.1).

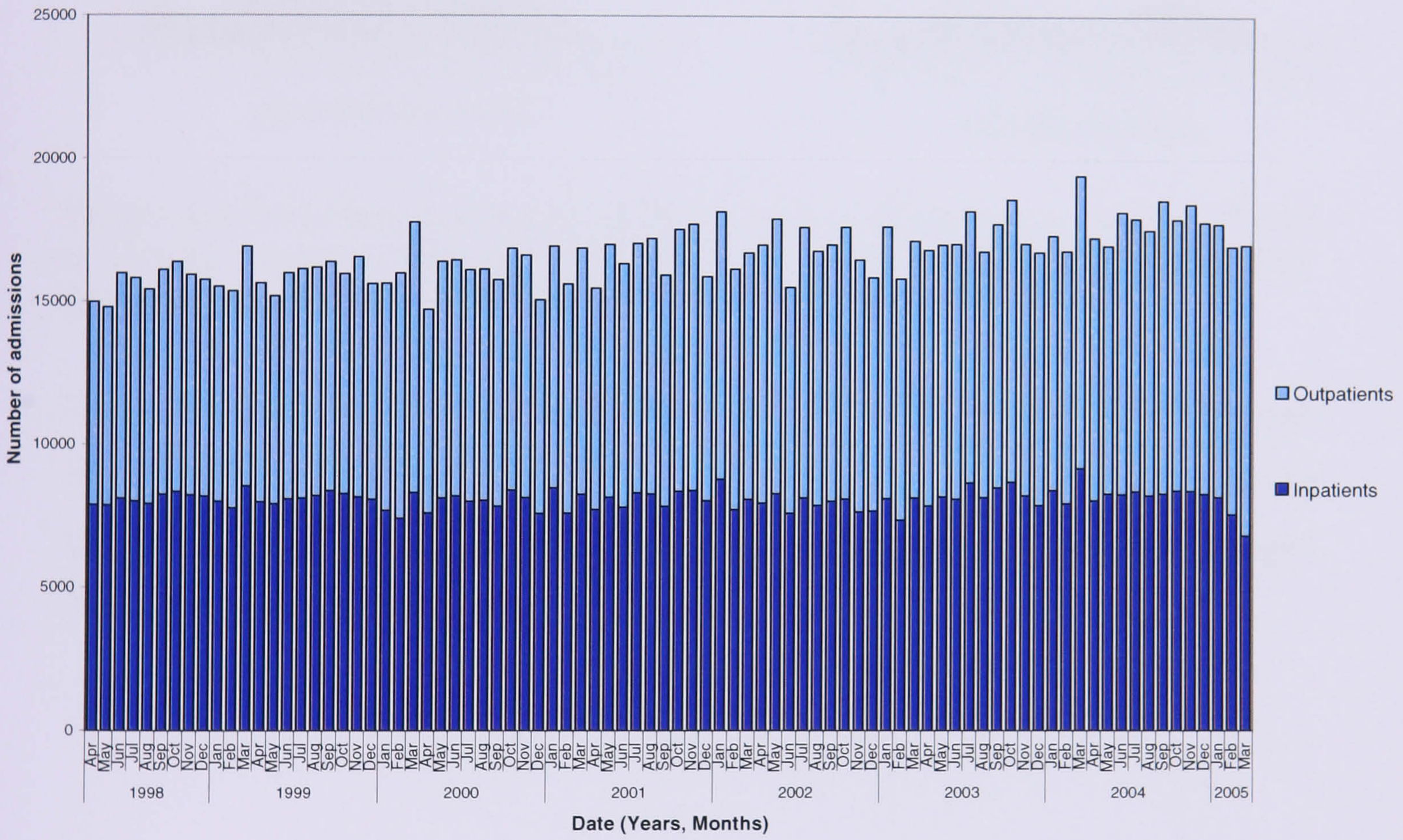



**Figure 4.1** Total number of admissions to the Trust per month from April 1998 to April 2005, includes both inpatient and outpatient admissions total n=1401471 and admissions by the inpatient group are distinguished, n=679588.

The ages of both inpatients and outpatients admitted to the Trust as well as the ages of inpatients only are shown in Figure 4.2; the distributions are similar in that ages range from 0 to 109 years with an age of 0 (i.e. including births) being the most common. In both cases the distributions are bimodal (if babies are excluded), however when outpatients are included the peak at around 30 years of age appears

more pronounced. On inclusion of the outpatient population the mean age of all admissions is marginally lower at 45.07, as opposed to 46.08 for inpatients.

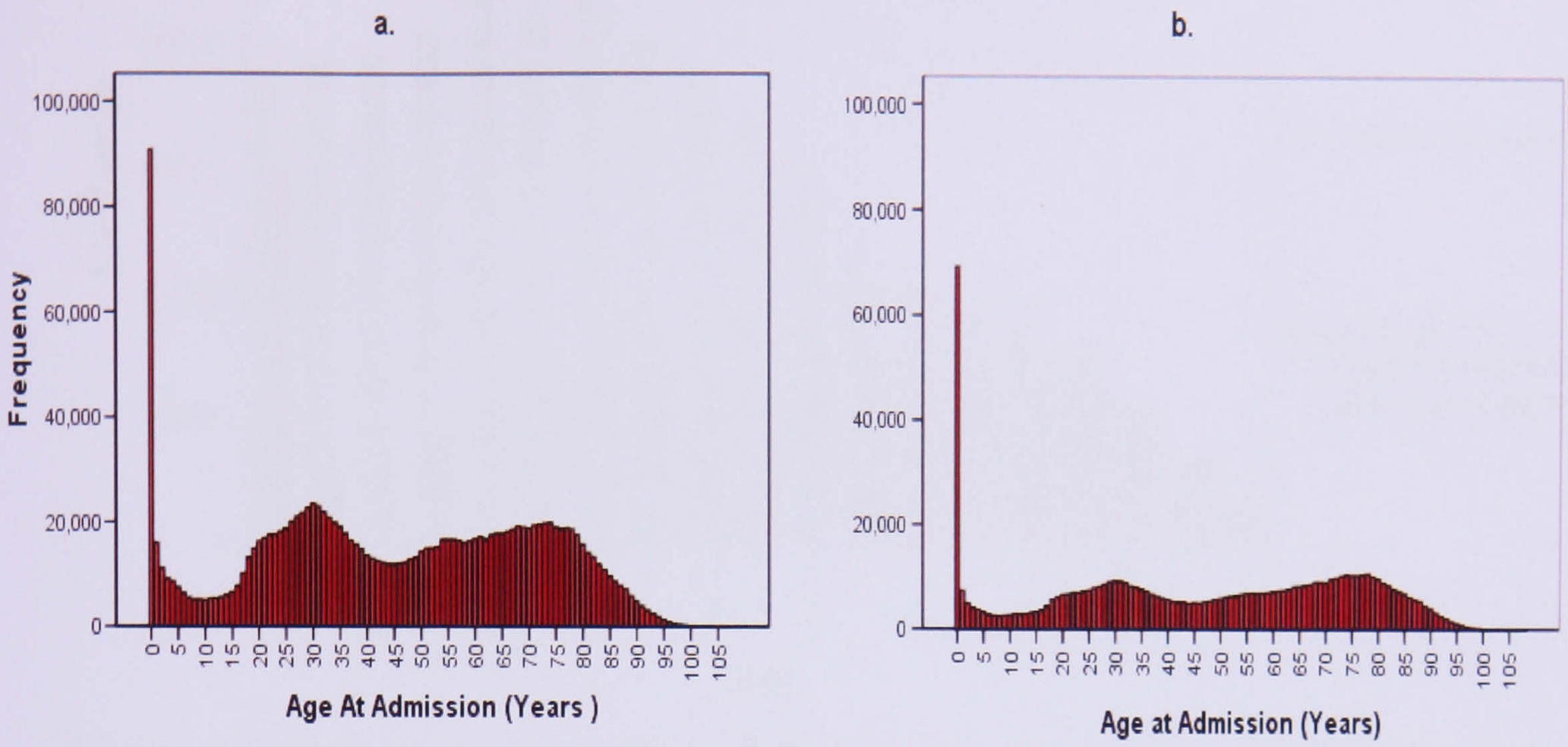



**Figure 4.2** Frequency distribution of patient age on admission to the Trust. Panel a) includes inpatient and outpatient admissions, n = 1401352, b) includes only inpatient admissions, n = 679508.

Figure 4.3 compares the age distribution of all hospital admissions to the age distribution obtained from the 2001 census. The very young (0-4 yrs) and the elderly are over-represented, children over 4 years, teenagers and middle aged adults are under-represented.

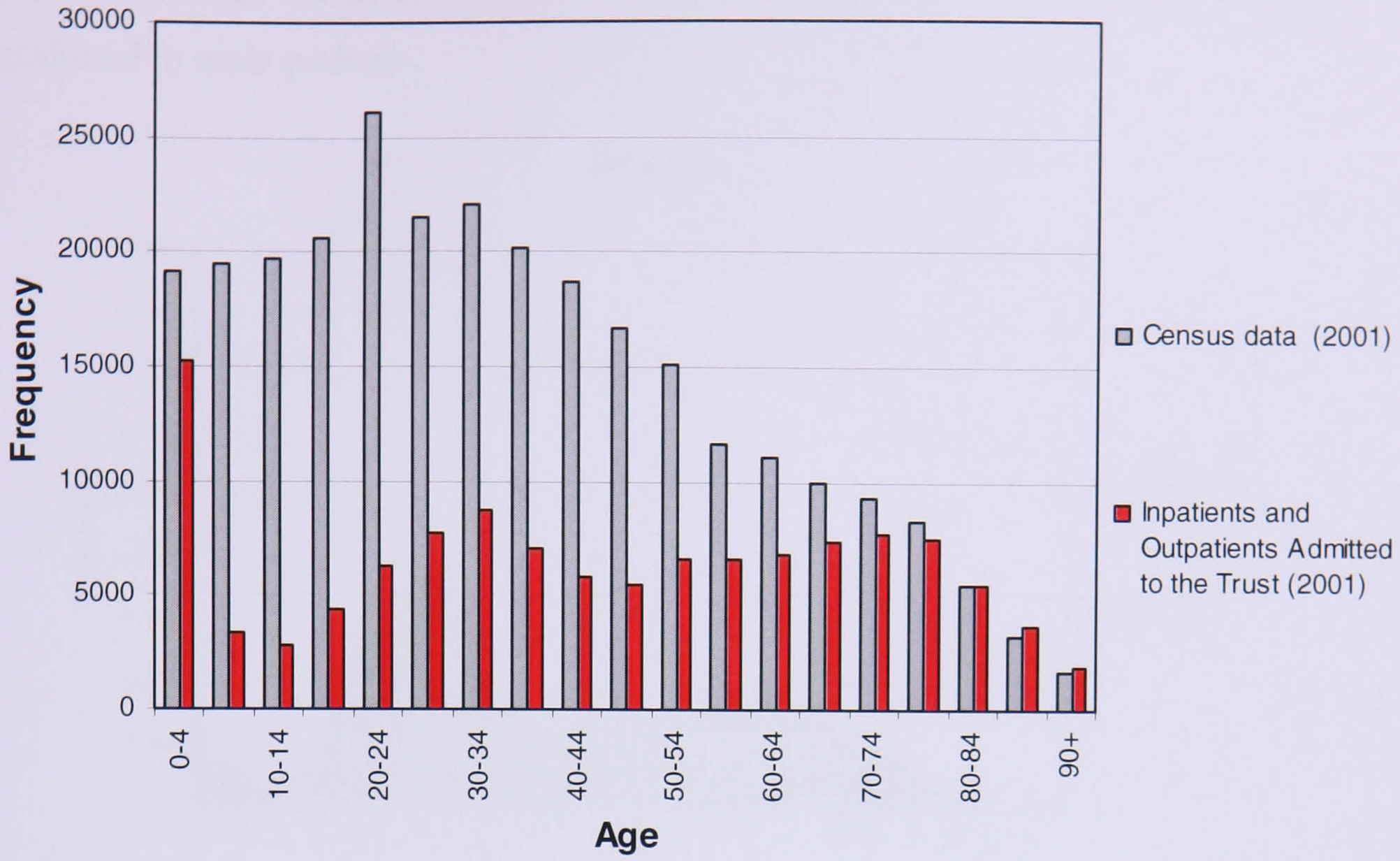



**Figure 4.3** Frequency distribution comparing ages of patients admitted to the Trust in 2001 (n=279921) to the age distribution of Leicestershire Unitary Authority obtained from the 2001 census (n=102587).

The frequency distribution of gender (Table 4.1) shows that the higher proportion of admissions to the Trust are female and that this is more marked when outpatients are considered. The 2001 census data states that a greater percentage of the population from the Leicestershire Unitary Authority is female (51.8%).

| **Gender** | **Frequency (both in- and outpatients)** | **Percent (of all admissions)** | **Frequency (inpatients only)** | **Percent (of inpatient admissions)** |
|---|---|---|---|---|
| Female | 810434 | 57.8% | 377435 | 55.5% |
| Male | 591027 | 42.2% | 302153 | 45.5% |
| Indeterminate | 6 | 0 | 0 | 0 |
| Total | 1401467 | 100% | 679588 | 100% |

**Table 4.1** Frequency distribution of gender of patients in the Trust, n= 1401467 for in and outpatients collectively and for inpatients only n = 679588.

The bimodal distribution of age at admission can be explained by splitting the age distribution by gender (Figure 4.4); the peak in age frequency at around 30 years

is due to female admissions and the peak in elderly admissions can be mainly attributed to male patients.

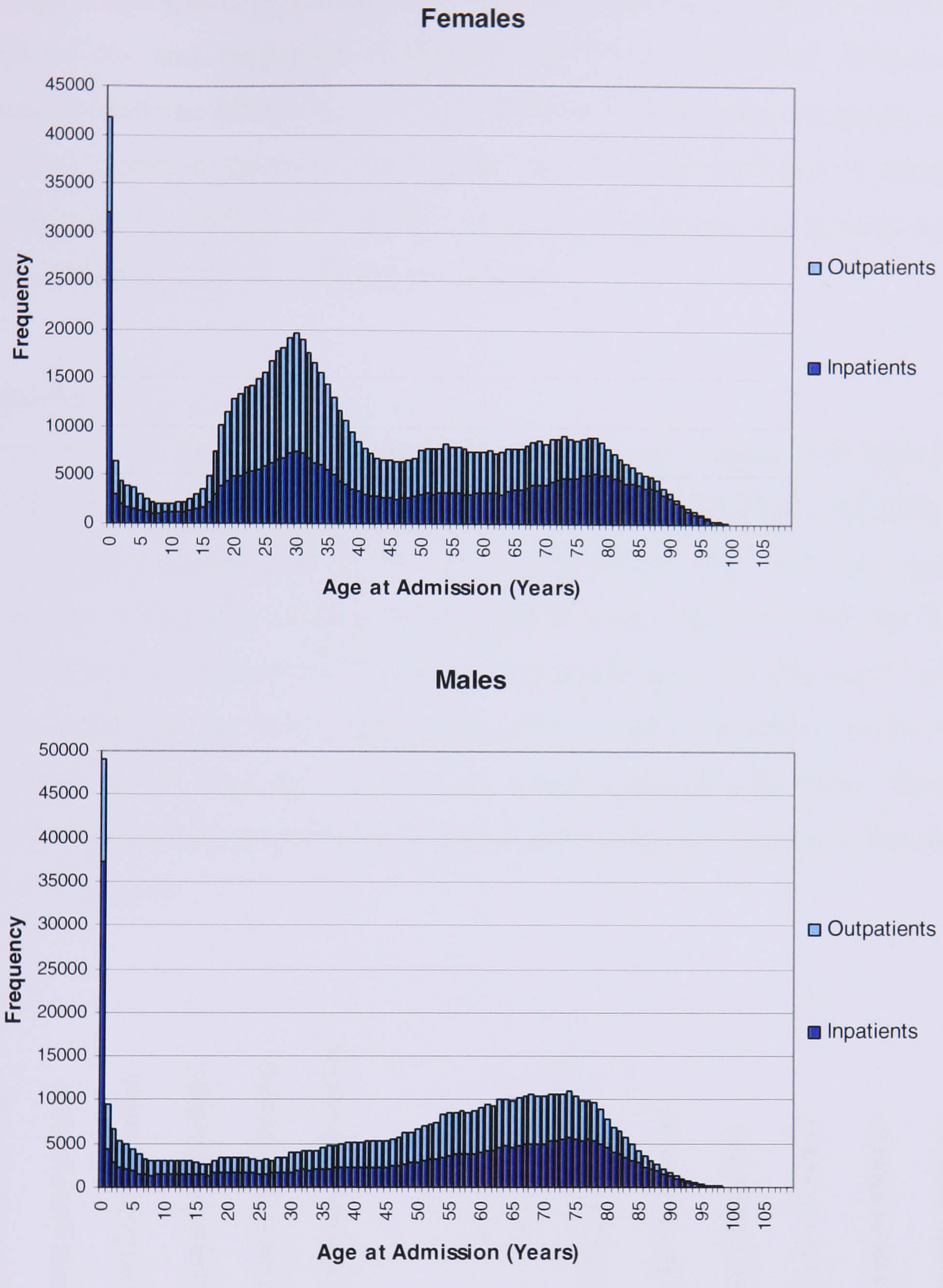



**Figure 4.4** Frequency distribution of ages of patients on admission to the Trust split by gender. The different panels show the distribution for female inpatient and outpatient admissions n= 810388 (inpatient admissions only, n=377406), and the distribution for male inpatient and outpatient admissions, n= 590954, (inpatient admissions, n= 302102).

There are 63 specialties within the three hospitals that make up the Leicester Trust; data on specialty is in terms of specialty from which the patient was

discharged. It is assumed that the specialty to which a patient is connected for a particular hospital stay is equivalent to the specialty from which they were discharged. The specialty discharged from most frequently is obstetrics making up 14.9% of in- and outpatient discharges (208121 of 1401471), followed by integrated medicine from which 14.1% (196940) of all hospital discharges occur. The most common specialty when only inpatients are included is integrated medicine (21.7%: 147237 of 679588), followed by obstetrics and general surgery (11.1%: 75368 and 10.3%: 69869 respectively).

**Hospital Level**

The number of admissions to each hospital by year (Figure 4.5) shows the majority of admissions to the Trust are to Leicester Royal Infirmary (LRI); in total this hospital encompasses 58.9% of all admissions and 53% of inpatient admissions. Admissions to Leicester General Hospital (LGH) account for 26.9% of the Trust's admissions and 29.8% of inpatient admissions. Glenfield General Hospital (GH) has the fewest yearly admissions of all the hospitals, 14.2% of all admissions to the Trust and 17.2% of the Trust's inpatient admissions. Numbers for 1998 and 2005 are lower for all hospitals due to the dataset only encompassing part of these years.

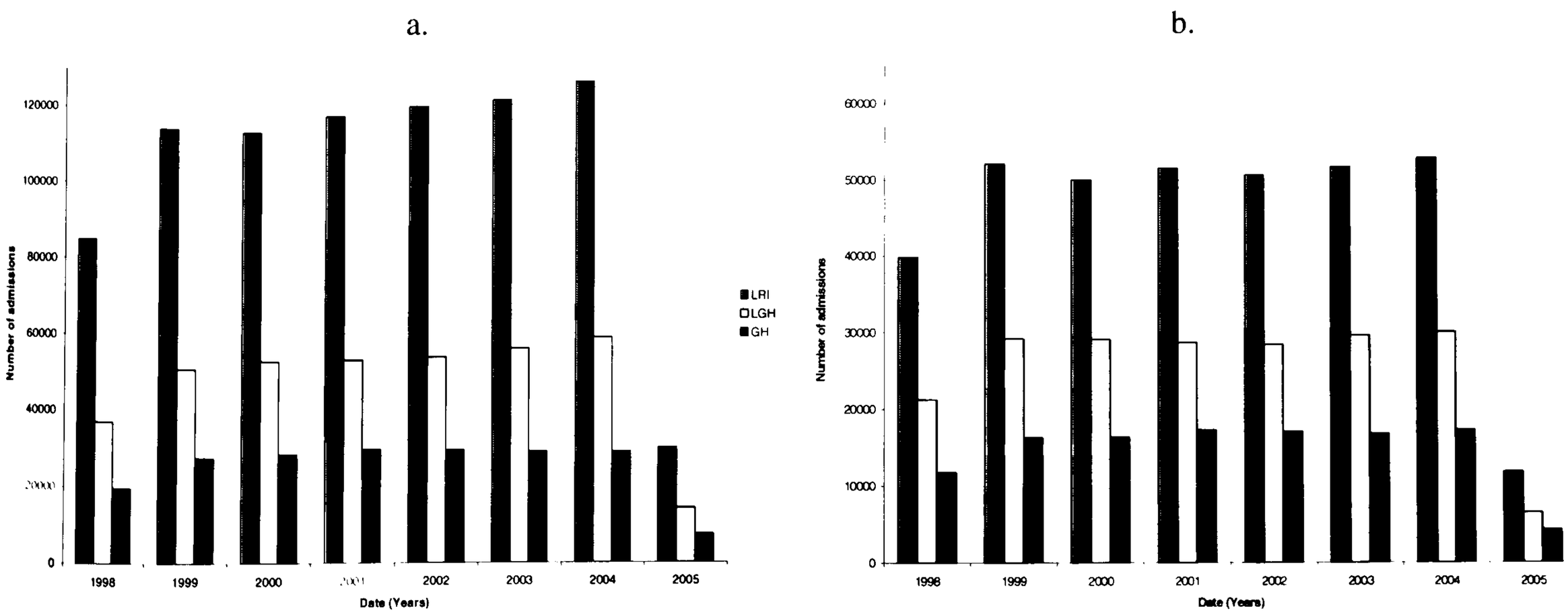



**Figure 4.5** Number of admissions to each hospital within the Trust by year from 1998 to 2005, a) includes both inpatient and outpatient admissions, n=1401471, b) includes inpatient admissions only, n = 679588.

The main differences in age distributions between each of the three hospitals (Figure 4.6) are that children are mainly seen at LRI, whereas patients under the age of 15 are rare for LGH and GH. However, patients of 0 years of age are common in both LRI and LGH. The distribution for GH shows an increase as age increases with a peak at approximately 60-70 years, showing that elderly patients are more common at GH.

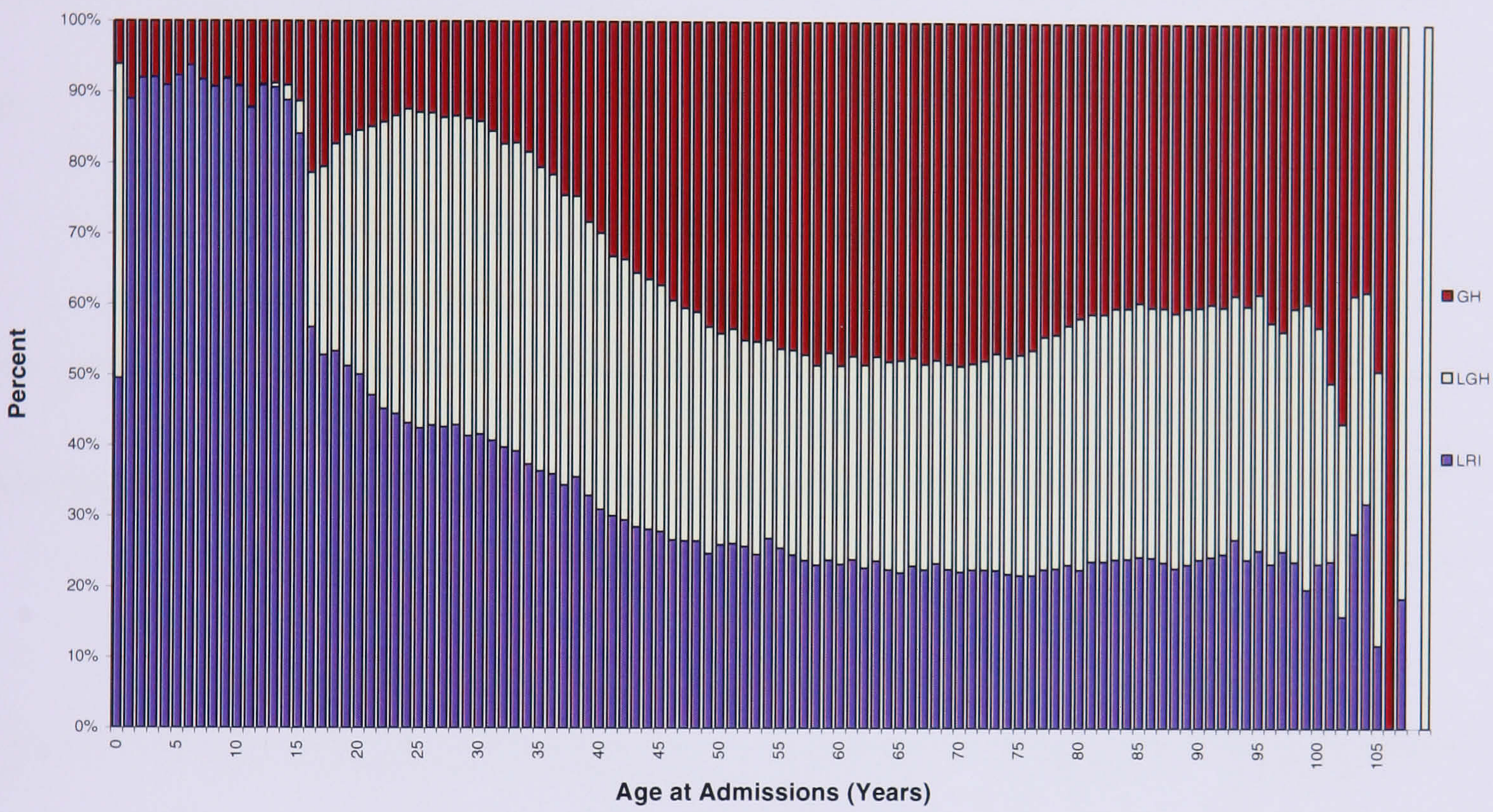



**Figure 4.6** Distribution of age groups between each hospital within the Trust, includes all admissions n=1401352 (for LRI n= 825499, for LGH n = 376320 and for GH n = 199533). Summary statistics for the age distribution of each hospital are given in Appendix 1 (Table A1.1).

Patients at LRI and LGH are more likely to be female than male (approximately 60% and 40% respectively for the entire hospital populations and approximately 57% and 43% for inpatients only), whereas a more even distribution is seen in GH (Table 4.2).

| | | Leicester Royal Infirmary | Leicester General Hospital | Glenfield General Hospital |
|---|---|---|---|---|
| Female | Freq. (including in- and outpatients) | 497165 | 216116 | 95439 |
| | Percent (of all patients) | 60.4 | 57.5 | 48.0 |
| | Freq. (including inpatients only) | 203807 | 115471 | 58157 |
| | Percent (of inpatients) | 56.6 | 57.0 | 49.8 |
| Male | Freq. (including in- and outpatients) | 326277 | 159412 | 103487 |
| | Percent (of all patients) | 39.6 | 42.4 | 52.0 |
| | Freq. (including inpatients only) | 156382 | 87032 | 58739 |
| | Percent (of inpatients) | 43.4 | 43.0 | 50.2 |
| Indeterminate | Freq. (including in- and outpatients) | 4 | 2 | 0 |
| | Percent (of all patients) | 0 | 0 | 0 |
| | Freq. (including inpatients only) | 0 | 0 | 0 |
| | Percent (of inpatients) | 0 | 0 | 0 |
| Total | Freq. (including in- and outpatients) | 823446 | 375530 | 198926 |
| | Freq. (including inpatients only) | 360189 | 202503 | 116896 |

**Table 4.2** Frequency distribution of the gender of patients at each hospital within the Trust, n=1397902 (for LRI n= 823446, for LGH n = 375530 and for GH n = 198926).

On comparison of the most common specialties for each of the three hospitals obstetrics can be seen to be the most common discharge specialty for LRI (17.4% of 825596 discharges) followed by integrated medicine (10.4%), clinical oncology (10.0%) and paediatric medicine (8.9%). Obstetrics and integrated medicine are also common in LGH together with urology (21.4%, 17.1% and 18.1% of 376341 discharges respectively). However, at GH, except integrated medicine (making up 15.6% of 199534 discharges), discharge specialties differ from those at the other

hospitals with the most common being cardiology (21.8%) along with general surgery (20.1%) and thoracic medicine (11%).

Looking specifically at inpatients, for LRI the most common specialty was integrated medicine, with 20.1% (72219 of 360189) of all inpatient discharges occurring from this specialty, followed by obstetrics and paediatric medicine, at 12.6% and 9.6% of discharges respectively. For LGH the most common specialty was integrated medicine (with 24.7% of 202503 discharges) followed by obstetrics, general surgery and urology (with 14.8%, 12.6% and 11.9% of discharges respectively). For GH the most common specialties were integrated medicine, general surgery, cardiology and thoracic medicine (with 21.3%, 17.8%, 17.1% and 14.2% of the 116896 discharges respectively).

**Transfers between hospitals**

If a transfer occurred during the hospital stay, the first hospital at which the patient stayed was taken to be the hospital they were admitted to. Transfers occurred in 0.25% of all admissions (3565 out of 1401471) and 0.52% of inpatient admissions (3526 of 679588). Tables of hospital transfers for both in- and outpatients and inpatients as a separate group are given in Appendix 1 (Tables A.2 and A.3).

### 4.3.2 Section B: Length of stay

**Trust Level**

The most common length of stay for a patient visiting the trust was 0 nights. However, due to the large range (0-1446 nights) the mean length of stay was 3.23 nights. The frequency distribution of length of stay (Figure 4.7) shows that stays were most frequently short, with the 75% quartile being at 3 nights. If outpatients are excluded from the analyses the mean length of stay increases to 6.65 nights and the 75% quartile to 7 nights. The remainder of analyses include only the inpatient population, as it is in this population where length of stay differs.

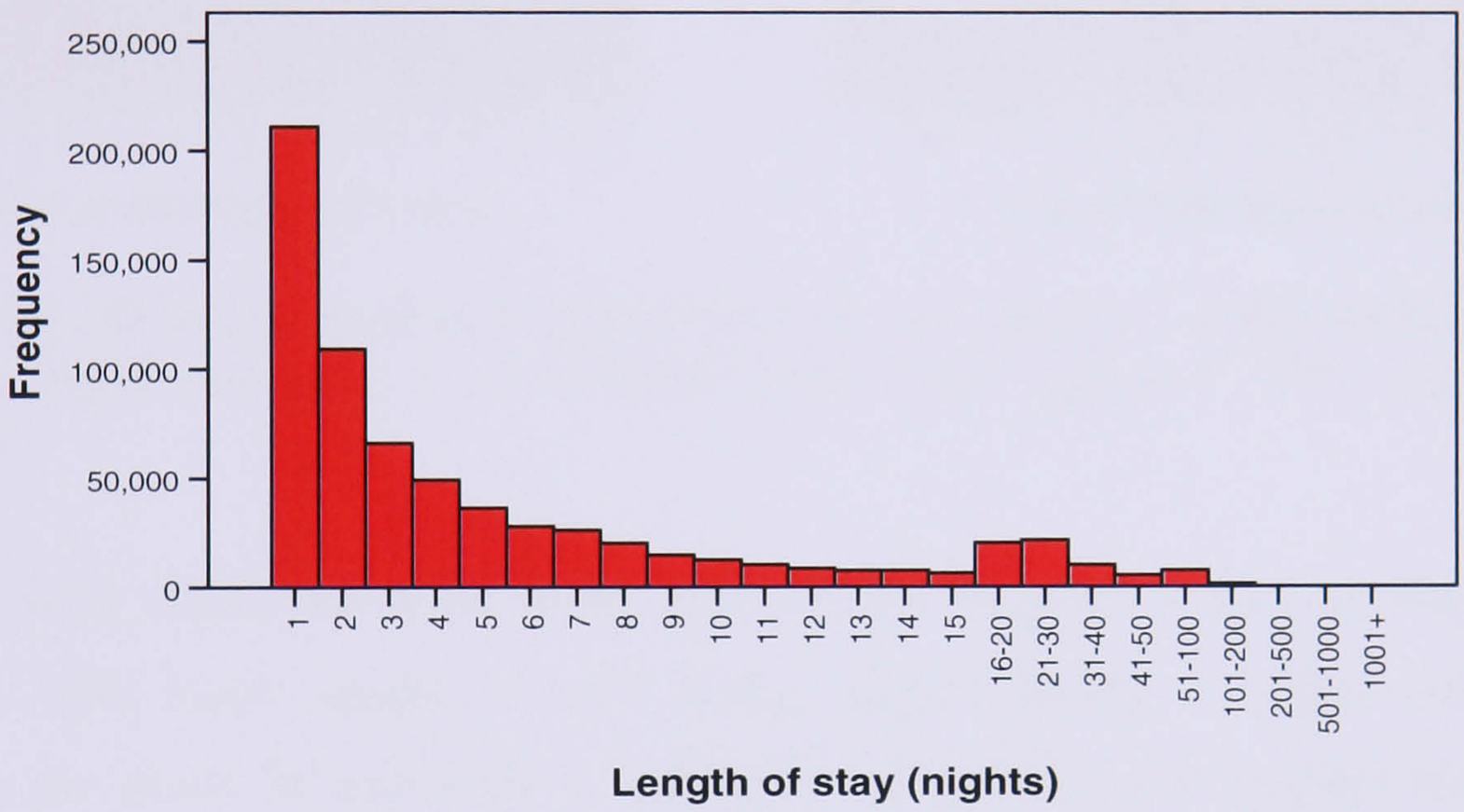



**Figure 4.7** Frequency distribution of inpatient's length of stay (given in nights) in the Trust's hospitals, n=679588.

The relationship between age and length of stay shows a 3-fold increase in mean length of stay with increasing age, a similar distribution is seen with median length of stay despite the summary statistics showing shorter stays due to the skewed data (Figure 4.8).

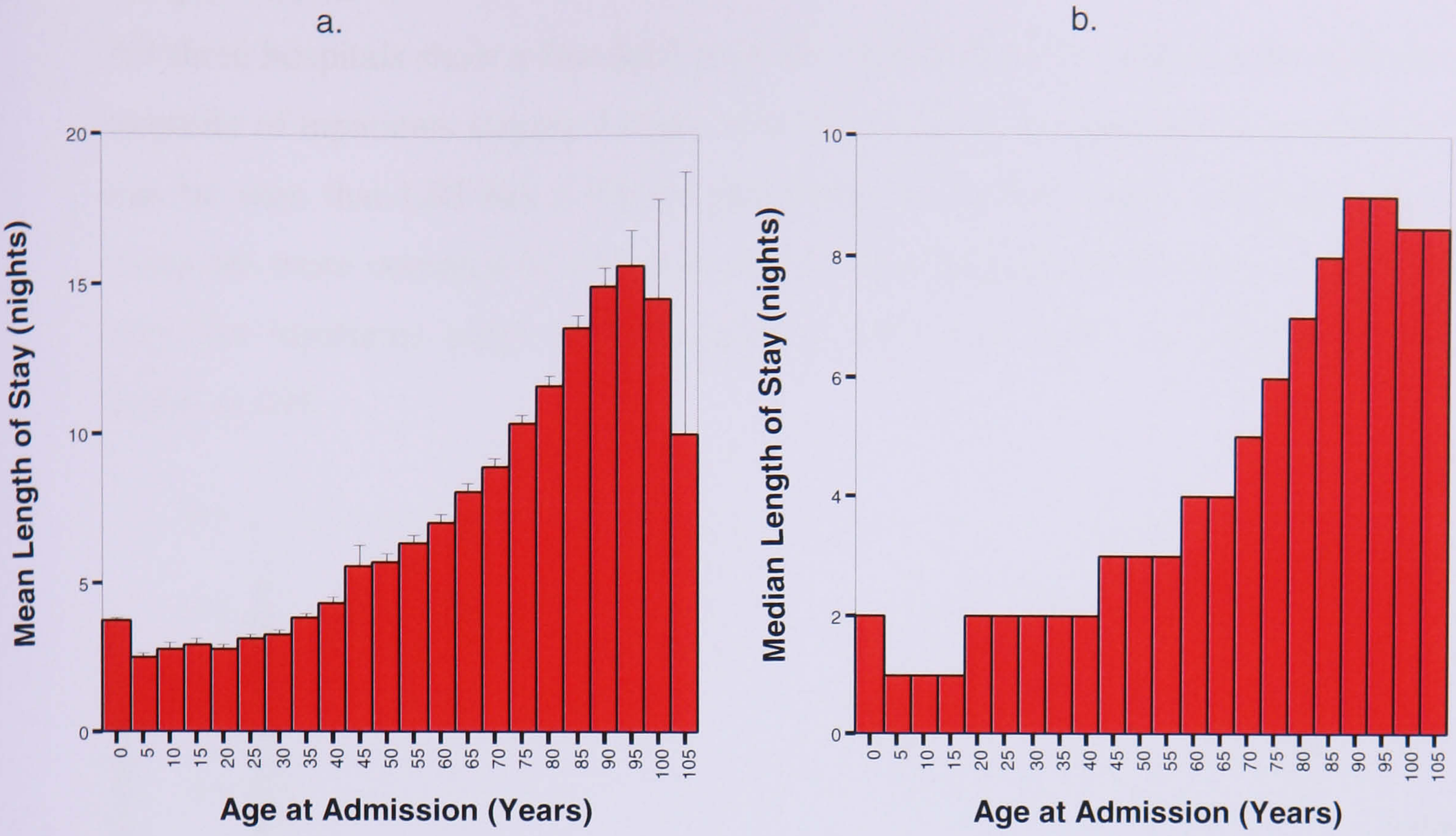



**Figure 4.8** Mean and median length of stay by age (panels a and b respectively), includes inpatients only, n = 679508. Error bars represent 95% confidence intervals.

Overall, little difference was found between the lengths of stay of males and females, with mean length of stay being approximately 3 nights (summary statistics are given in Appendix 1, Table A1.4). Splitting the hospital stays into those by males and those by females, and exploring the length of stay by age based on these demographic groups gave very similar results, however females in older age categories were shown to have slightly longer stays (Figure A.1, Appendix 1). The relationship between specialty and length of stay was also investigated and the longest stays (in nights) corresponded to rehabilitation, with rehabilitation of the elderly having a mean length of stay of nearly 48 nights (n=1401471, all admissions). Given that females of ages 15-40 years constituted such a large proportion of hospital admissions, specialties associated with these patients were also explored, with mean length of stay for obstetrics being 1.04 nights (n= 208121) and gynaecology 1.21 nights (n = 80189).

**Hospital Level**

All three hospitals show a fast decline in the distribution of length of stay with the majority of inpatients staying 1 night only (Figure 4.9). Comparing the hospitals it can be seen that LRI has a higher percentage of shorter visits, whereas longer visits are more common in GH than in the other hospitals with mean lengths of stay (for inpatients only) of 5.75 nights at LRI, 7.16 nights at LGH and 8.55 nights at GH.

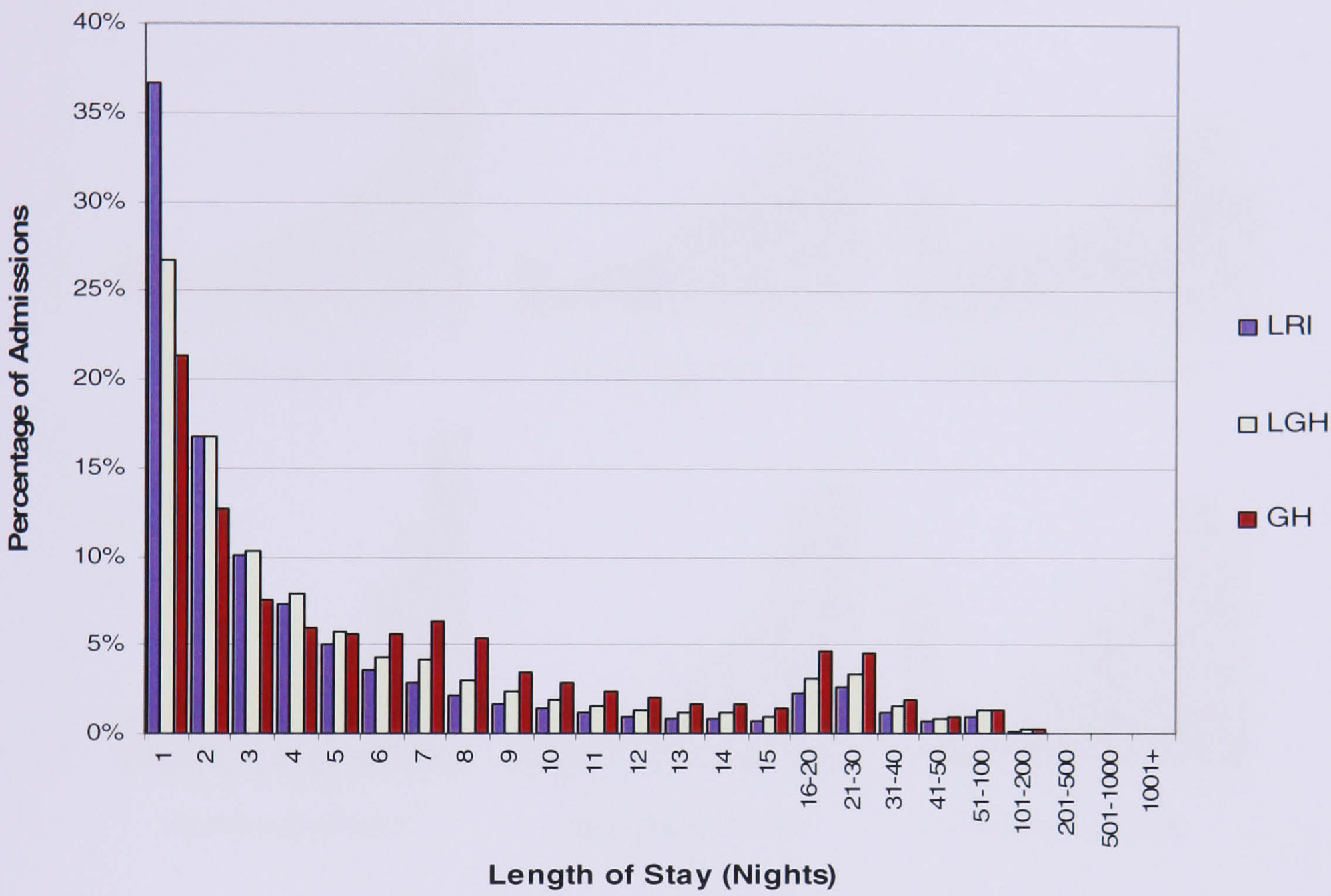



**Figure 4.9** Frequency distribution of the patient's length of stay at each hospital within the Trust, includes inpatients only, n=679588 (for LRI n=360189, for LGH n=202503 and for GH n=116896).

At an individual hospital level, length of stay by age at admission largely reflects that for the Trust as a whole. However, the length of stay for patients below 50 years is generally longer at GH than the other hospitals, especially for infants. The distributions of length of stay of the inpatient population by age at each hospital can be seen in Figure 4.10. Again, little difference was found between the lengths of stay of females compared to males for each hospital: having a mean of 2.39 nights and 2.69 nights respectively at LRI; 3.66 nights and 4.11 nights at LGH and 5.36 nights and 4.69 nights at GH (full summary statistics are given in

Appendix 1, Table A1.5). The investigations into length of stay in relationship to specialty showed that for all patients the specialties associated with the longest hospitals stays were rehabilitation (for LRI with a mean length of stay of 48 nights) and rehabilitation and care of the elderly (for LGH and GH with mean lengths of stay for this specialty of 48 and 51 nights respectively).

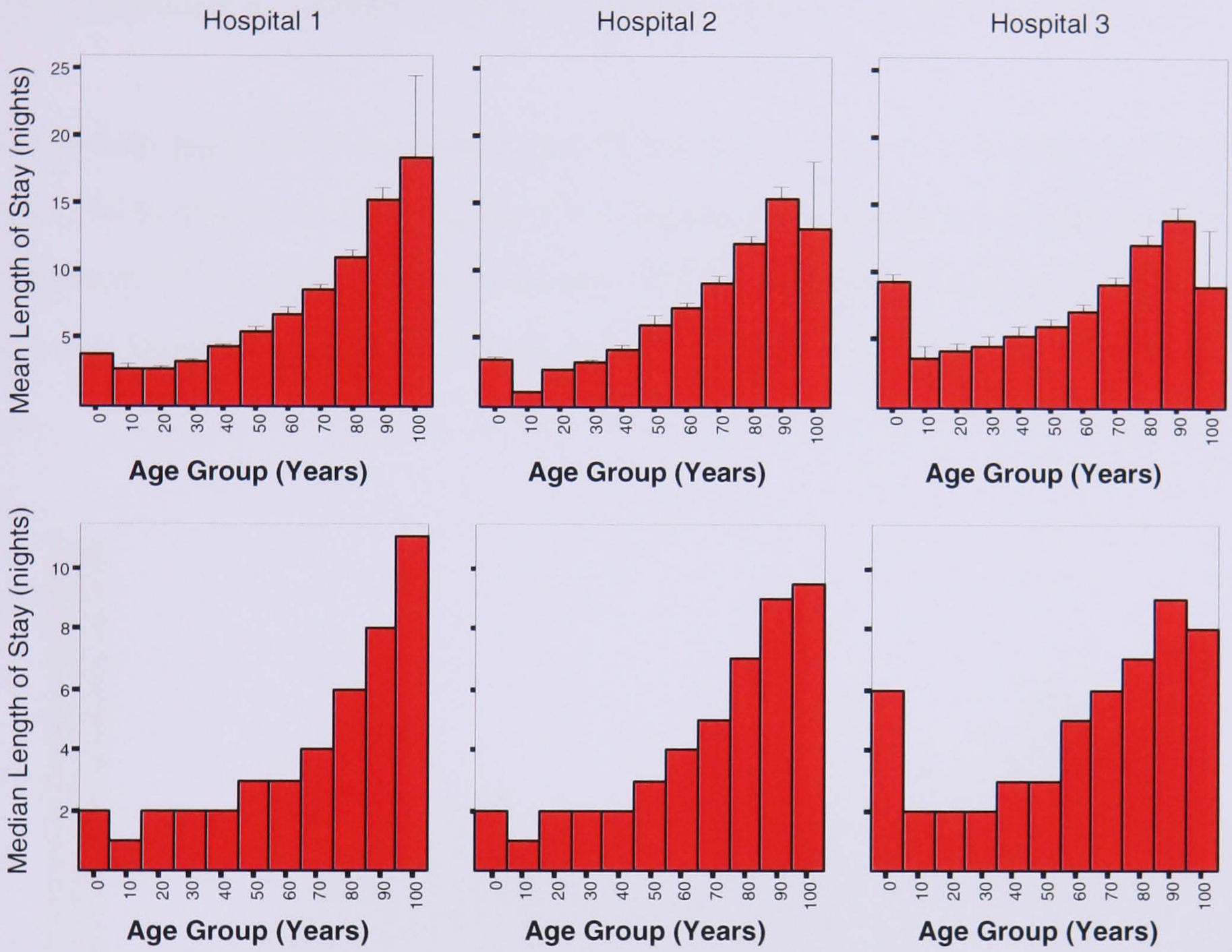



**Figure 4.10** Frequency distribution of the patient's length of stay (mean, top row and median, bottom row) by age group at admission for each hospital within the Trust, includes inpatients only. Where, Hospital 1 =LRI, n=360127, Hospital 2 = LGH, n= 202486 and Hospital 3 = GH, n=116895.

### 4.3.3 Section C: Patient population

**Trust Level**

Demographic characteristics of the patient population were determined by establishing patients who were in hospital on any day(s) during March 2001, 2002 and/or 2003. Note that the same patient may be included more than once if they were readmitted in a different year or changed category between readmissions.

The patient population is slightly biased towards females consistently over the 3 years. With respect to age (Figure 4.11) the patient population is largely made up of patients of the age groups 0-4years, 20-35 years and 70-85 years. The most variation in age distribution between years was seen in the older age categories.

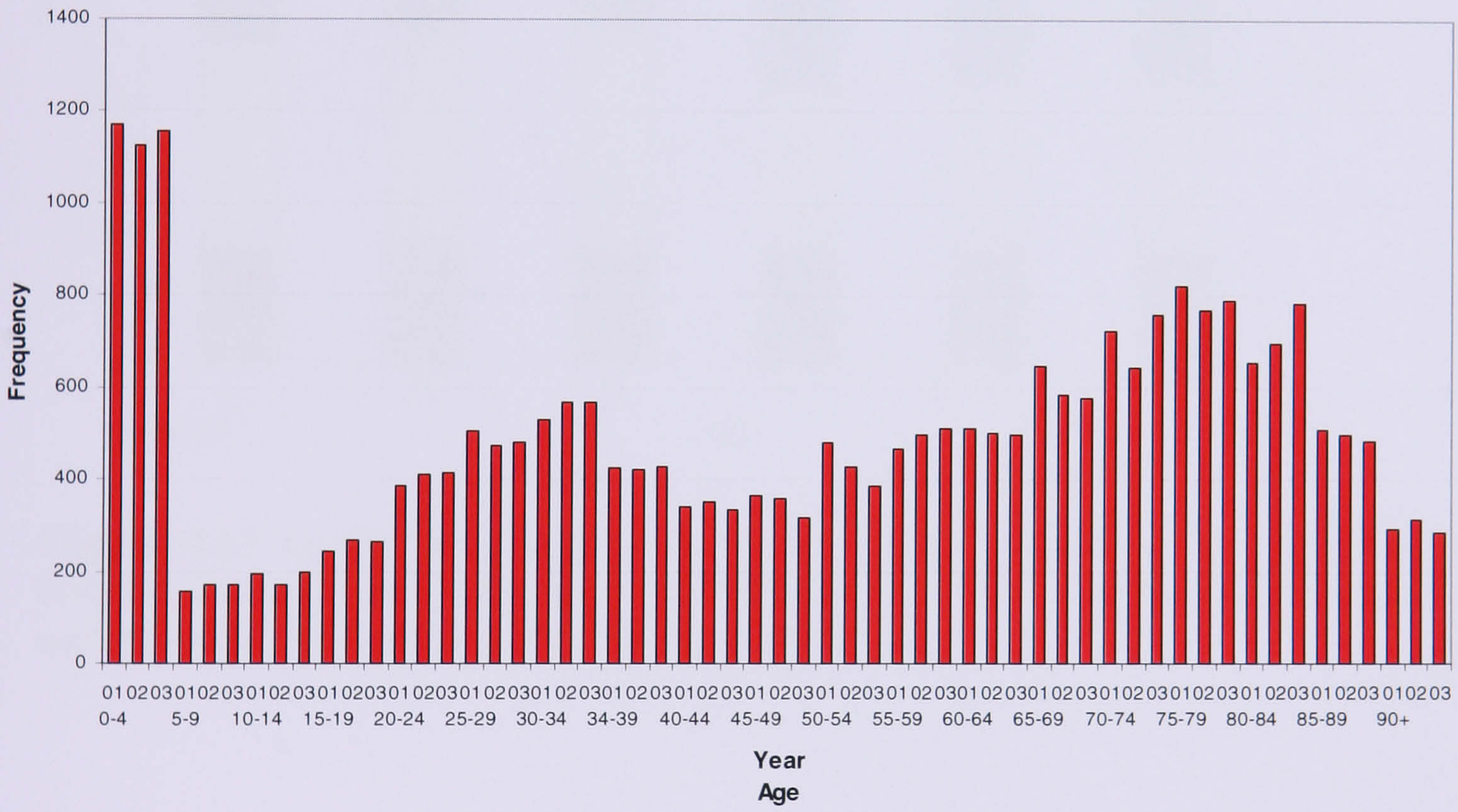



**Figure 4.11** Age group representations in the Trust's patient population during March 2001, 2002 and 2003 (n = 28090, the numbers of patients in each age band seen during March 2001, 2002 and 2003).

**Hospital Level**

From the hospital level analyses it is clear that the populations in LRI and LGH have a slightly greater proportion of female patients, whereas there is little difference in gender representation at GH (Figure 4.12). With respect to representation of different age groups within the patient populations (Figure 4.13)

the vast majority of patients of less than 20 years are seen at LRI, where an approximately even distribution is seen throughout the other age groups. The population at LGH is made up of either infants (0-4 years) or patients of 15 years or above. The population of GH is largely made up of patients of older age groups, with 50-85 years olds being the most common.

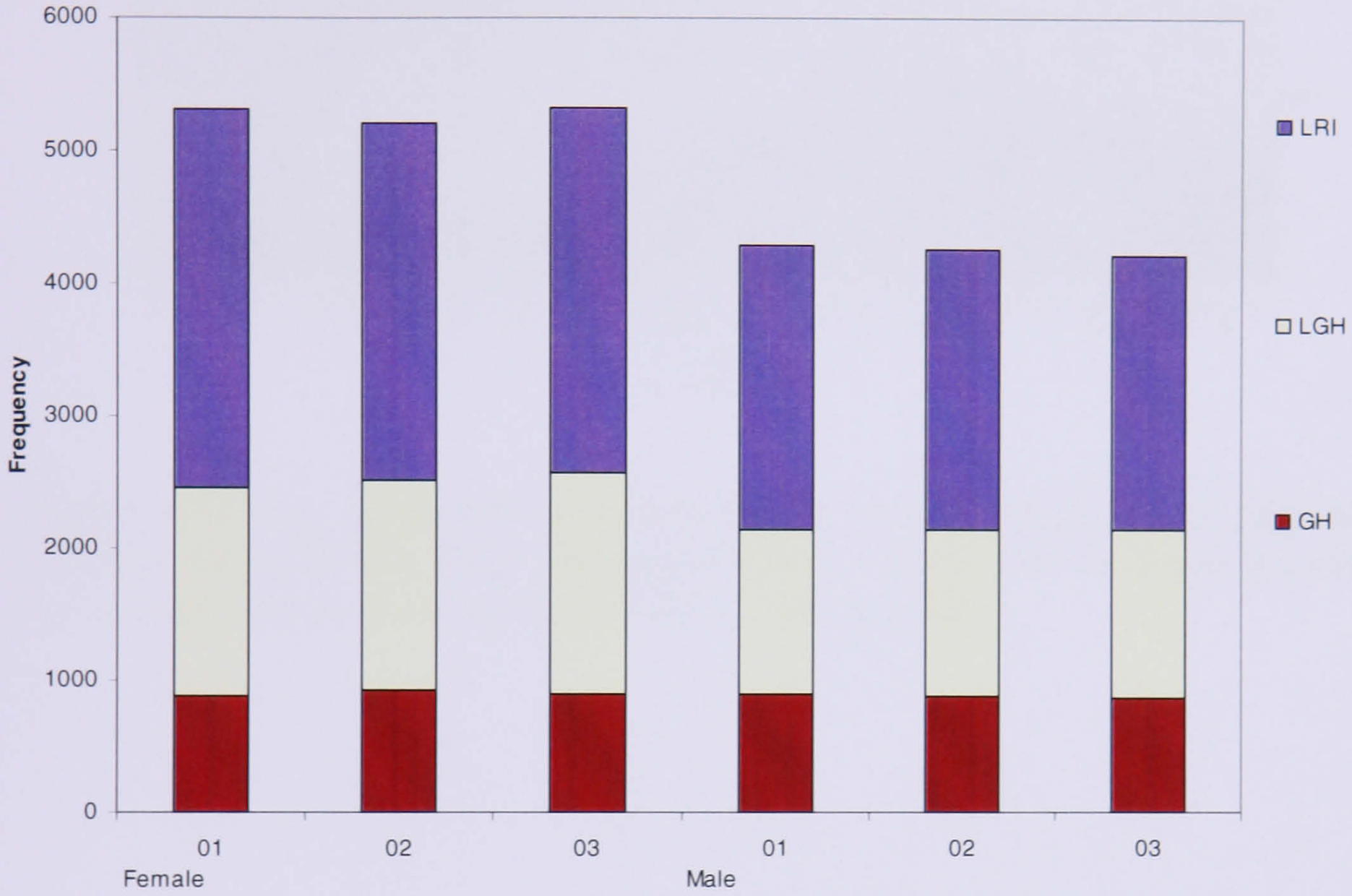



**Figure 4.12** Gender representations in the patient population of individual hospitals during March 2001, 2002 and 2003 (n=28613, the numbers of patients of each sex seen in March of 2001, 2002 and 2003).

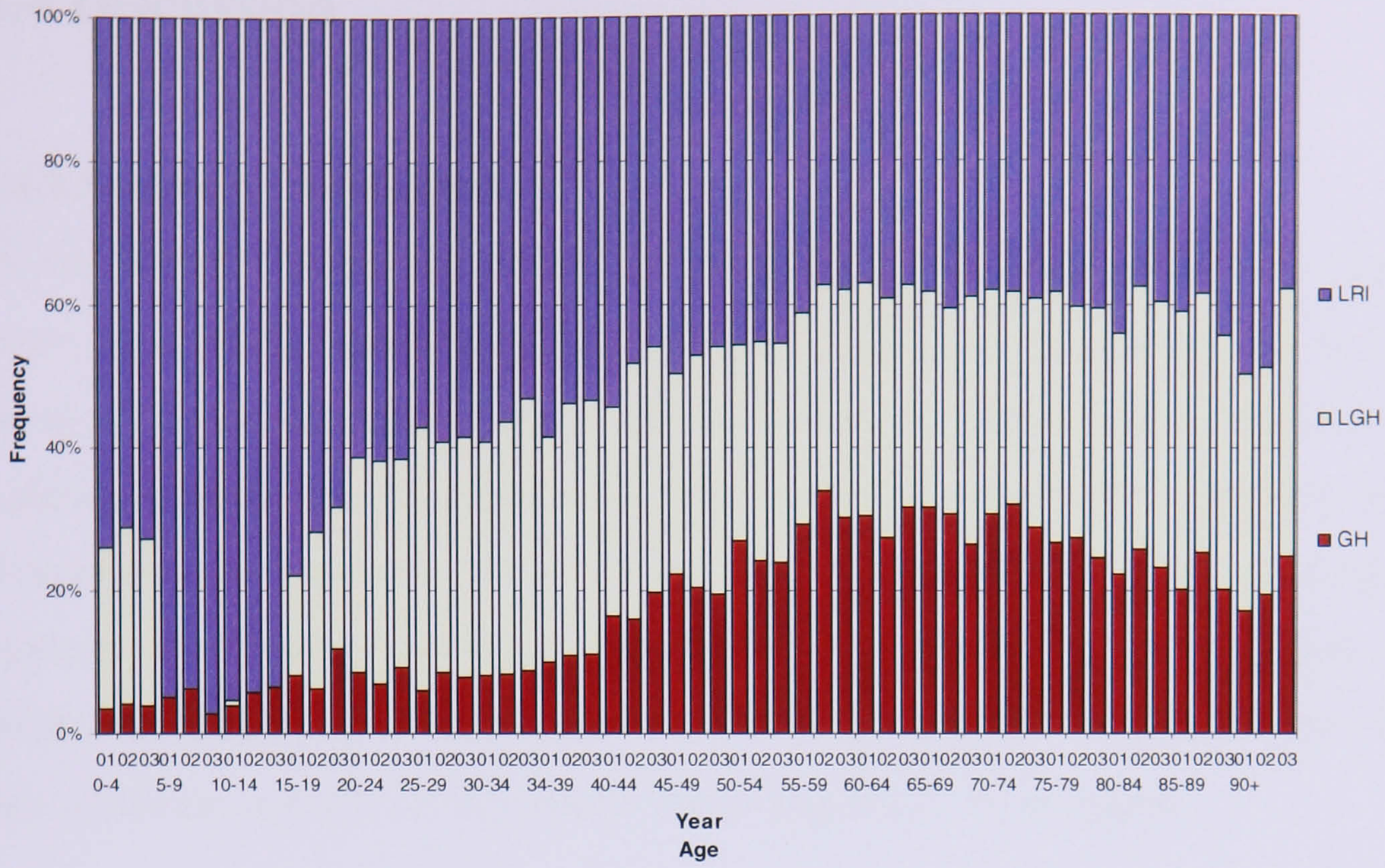



**Figure 4.13** Age group representations in the patient population of individual hospitals during March 2001, 2002 and 2003 (n = 28622, the numbers of patients in each age band seen during March 2001, 2002 and 2003).

## 4.4 Discussion

### 4.4.1 Section A: Admissions

Of the 1401471 admission events the vast majority of admissions were aged 0 years, most likely representing births (Figure 4.2). This corresponds to obstetrics being the most common discharge specialty. There is also a peak in admission of patients in their late 20's and early 30's (which is particularly apparent when outpatients are included) (Figure 4.2), most likely corresponding to pregnant mothers, as is backed up by the age distributions split by gender in Figure 4.4. Additionally there is a peak in admissions at approximately 80 years (Figure 4.2), this would be expected as the elderly more frequently visit hospital.

In the comparison of patient demographics to the demographics of the Leicestershire area it may be concluded that in terms of age, babies and the elderly were highly represented within the Trust (Figure 4.3) and in terms of gender females were highly represented (Table 4.1). As the demographic groups of the very young and very old are often the most susceptible to infection, the high representation of these age groups within the hospital population is likely to have consequences in infection control policy design. The overrepresentation of females may be due to pregnant mothers who, therefore, may pose more of an infection risk than previously suspected. However, the fact that admittees of this age group are often outpatients may serve to reduce the threat.

Demographics of the admission population may differ considerably between hospitals. For example, the age distribution of the admission population seen at the Trust level (Figure 4.2) is not mirrored at each individual hospital and there is clearly an age bias for each hospital (Figure 4.6). Patients in the 5-10 year age category have approximately a 90% chance of admitting LRI, where as 60-65 year olds are most likely to be admitted to GH. These differences in age distributions may be explained by the specialty distributions for each hospital: whilst paediatrics was common at LRI, specialties associated with older age groups (e.g. cardiology) were common at GH. Similarly, each hospital had a slightly different

distribution regarding gender (Table 4.2). For example, GH had a slightly lower proportion female admissions than male admissions (48% for in- and outpatients) whereas the opposite was true for the other two hospitals, the distinct lack of admissions of patients of 20-30 years (Figure 4.6), which was seen in the other two hospitals, may correspond to few admissions of child-bearing women and therefore low numbers of female patients. Moreover, a decrease in admissions of child-bearing women would mean fewer births, explaining the markedly lower percentage of admissions of 0 year olds (Figure 4.6).

These differences in the demographics of the admission populations may have implications in infection control in that hospitals with higher probabilities of admitting higher risk patients could be targeted as an infection control priority.

Additionally, an important consideration regarding the influence of patient admission patterns on infection control may be the distinction between inpatient and outpatient admissions. The potential risks posed by these two groups may differ considerably depending on differences such as staff and patient mixing patterns both within and between groups.

### 4.4.2 Section B: Length of stay

Most hospital stays were short (Figure 4.7) with 75% of visits being for less than 4 nights and the vast majority of patients being outpatients. With regards to infection control this may equate to a smaller risk of contracting a HCAI.

Length of stay generally increases with age (excluding infants) (Figure 4.8). The drop in mean length of stay in patients greater than 100 years may be due to the higher death rate in the very elderly, however the confidence interval associated with this result is large making any inferences spurious. The finding that length of hospital stay is greatest for the elderly is corroborated by the relationship between length of stay and specialty where, as may be expected, rehabilitation and care of the elderly was associated with the longest stays. Similarly the relationship between age and length of stay may also tally with the hospital level distributions

seen in Figure 4.9, which show that on comparison of the three hospitals LRI was associated with shorter hospital stays and GH was associated with longer stays. This is to be expected if considered with the age distributions for each hospital (Figure 4.6) where LRI is associated with younger age groups and GH is associated with older age groups.

Such confounding factors need to be considered in the design of an infection control strategies, for example if elderly patients are more common then longer hospital stays are more likely which is a known risk factor for HCAI (Graffunder and Venezia, 2002; Safdar and Maki, 2002) and due care and attention needs to be paid to the presence of this risk group.

### 4.4.3 Section C: Patient population

The representation of different demographic groups within the patient population is dependent not only on admission frequencies, but also the associated length of stay.

Despite there being little difference in length of stay between males and females overall more females were admitted to the Trust (especially in the 20-30 year age category) (Figure 4.4) meaning the Trusts population was slightly biased towards female patients. Similarly, despite the relatively short length of stay of infants and 20-30 year olds (Figure 4.8) the vast numbers of admissions of these age groups (Figure 4.2) meant they were still highly represented within the patient population (Figure 4.11). The relatively high numbers of admissions of elderly patients, coupled with their lengthy stays meant that elderly patients consistently made up a large proportion of the Trust's population (Figure 4.11).

From the hospital level results, it becomes clear that the slightly higher female representations are associated with those hospitals that have a higher proportion of younger patients within their population (namely LRI and LGH). Again, linking to the peak in female admissions in the 20-30 year age category (Figure 4.4).

Whereas hospitals with an older patient population have a more evenly distributed gender representation (GH) (Figures 4.12 and 4.13).

From these patient demographic distributions, again infants and the elderly are highlighted as a potential infection control risk due to their high representation within the population. However, perhaps more surprisingly, young females (20-30 years) are shown to make up a considerable proportion of the population despite being associated with some of the shortest stays, and may therefore prove to be, a previously overlooked, high priority demographic group in terms of infection control. This may be a particular risk for infection with high transmissibility where short hospitals stays will be less of a limitation on infection spread.

This chapter has demonstrated that even a simple presentation of basic patient demographics highlights a number of interesting findings with many implications, especially with regards to infection control.

# Chapter 5

# An estimate of the impact of heterogeneity in readmission rates in transmission dynamics of healthcare-associated infections

## 5.1 Introduction

Theoretical modelling has shown that patient movements in and out of hospitals are likely to affect nosocomial transmission dynamics considerably. The community acts as a "reservoir" and readmission of individuals colonized during previous admissions can result in sporadic transmission episodes within hospitals. These transmissions distributed over multiple hospital admissions may have a considerable effect on the benefit of infection control practices. Information on patient movements in and out of hospital and flow around the healthcare system would be of value in furthering our knowledge of infectious disease transmission and control.

In this chapter, patient movement patterns are investigated and the frequency with which hospital readmissions occur determined using a 7 year dataset from the UHL NHS Trust. Sufficient information is held on individual patients to study the

heterogeneity in readmission. Another interesting aspect of this dataset is that it includes admissions and discharges to and from the three hospitals within the Trust that serve a defined population. Therefore, movements around the whole healthcare system can be studied. To the author's knowledge this is the first attempt to describe hospital demographics in a multi-centre setting.

Basic summary statistics and frequency distributions are presented exploring differences in readmission patterns for the Trust as a whole as well as on an individual hospital level. In addition, results in terms of the probability of an infected patient being readmitted while still infected are presented. Direct estimates of this probability are obtained from the dataset and the relationships with demographic groups are investigated. The majority of the findings in this chapter are published (Robotham *et al.*, 2007b) and have been presented at the Sixth International Conference of the Hospital Infection Society, Amsterdam, Netherlands (2006).

### 5.1.1 Importance of the community and readmission

A number of studies have investigated the importance of the community population in terms of the transmission dynamics of HCAI. Cooper *et al.* (2004a) explain how control policies (particularly those largely made up of increased hand hygiene and patient isolation) have had mixed success. They describe how in some cases control measures have contributed to infection control, whereas in other settings the same measures have failed. They use a stochastic mathematical model to explore potential reasons for these differences and investigate conditions under which policies are likely to succeed. They find that if the pathogen can be carried asymptomatically (such as with MRSA), and over long periods of time, then transmission may be distributed over several hospital admissions, i.e. readmitting patients reintroduces sources of infection to the hospital. They find that this reintroduction of infection through readmissions may be sufficient to cause an epidemic, especially if the infected individual is brought into an entirely susceptible population. Therefore readmissions have an effect of prolonging infection within hospitals, and introduce an inherent time delay; the prevalence of

infection at admission is determined by hospital transmission many months previously. As a consequence, control policies which reduce secondary cases for a single admission only, despite short term control, may not prevent infection becoming endemic in the longer term. They further highlight the importance of the community and surrounding hospital network with respect to control success/failure, in that control failure at neighbouring hospitals may give rise to an increase in cases through hospital transfers or overlapping catchment areas.

Similarly, Smith *et al.* (2004) describe how even if hospitals reduce incidence of infection (i.e. the rate of new cases), prevalence of infection/colonization may not reduce due to the admission of carriers from populations outside the hospital such as the community, other hospitals and long-term care facilities. They use structured population models to explore the consequences of persistent colonization and demonstrate how an epidemic within one hospital may cause an increase in prevalence to other hospitals and the community population, i.e. its own catchment population. They describe how consideration of this accumulation of carriers in the catchment population is important to control, suggesting that control measures should be regionally coordinated and patient movement patterns, around the network, tracked (especially HCW, frequent and recent admittees, and long-term patients).

In another study, Smith *et al.* (2005) investigate the economic incentives and population biology of hospital infection control. They find that a hospital's infection control strategy should be influenced by the proportion of positive admissions, highlighting the importance of the community as a reservoir of infection, and also by the strategies of the surrounding hospitals, again highlighting the importance of consideration of the whole healthcare network.

Pittet *et al.* (1996) confirmed that approximately one third of all patients harbouring MRSA during one hospital stay remained persistent carriers and were still MRSA positive upon readmission. They proposed that an admission identification list of all patients positive for MRSA during their previous stay

would have allowed identification upon readmission. leading to immediate identification of at least a third of the hospital prevalence. Sébille and Valleron (1997) suggest that it is the admission of these infected or colonized patients that is associated not only with the initiation of outbreaks, but also the perpetuation of epidemic behaviour.

In addition, earlier work in this thesis (Chapter 3), building on that of Cooper *et al.* (2003; 2004a), explored surveillance and control strategies in a framework including both hospital and community populations. Whilst inpatient screening controlled transmission within the hospital which translated to community control, admission screening failed to reduce transmission within the hospital and allowed community infection level build up. Only once community infection levels became sufficiently high (i.e. a sufficient proportion of readmitted patients were infected/colonized) did admission screening become effective. This showed that there is interplay between control within the hospital and control within the community population and that community infection levels can determine the success of a control strategy.

Despite these studies theoretically describing the importance of movement between the hospital and community, to the authors' knowledge, there are no studies using observed movements to and from the hospital and community, particularly with respect to patient readmission patterns. Knowledge of factors such as what proportion of patients are likely to come back into hospital after discharge, how many times they are likely to be admitted to hospital, how long it is likely to be between each admission, how long they are likely to spend in hospital on each admission and so on, would be of great benefit. Furthermore, with a growing body of evidence suggesting that CA-MRSA can be transmitted within the hospital and similarly hospital-associated MRSA within the community (Calfee *et al.*, 2003) and with the apparent increase of CA-MRSA (Fridkin *et al.*, 2005) the importance of investigating the patterns of patient movement between hospitals and communities is all the more crucial.

For the purposes of this thesis an increased understanding of such movement patterns would most importantly inform the transmission dynamics of HCAI such as MRSA and *C. difficile*, providing a better basis from which to design control strategies. In view of the lack of studies into the patterns of patient flow between the hospital and community, here hospital data from the UHL NHS Trust spanning seven years 1998-2005 is analysed.

### 5.1.2 Importance of readmissions in terms of $R_0$

Previous work investigating nosocomial transmission dynamics and screening strategies with respect to both the hospital and community populations (Cooper *et al.*, 2003; Cooper *et al.*, 2004a and the work introduced in Chapter 2) considered transmission in two inter-related, but differentiated aspects: transmission within the hospital and transmission considering movement between the hospital and community populations i.e. transmission caused by multiple returns to hospital. As previously described, both can be considered in terms of basic reproduction numbers; in the simplest model, the within-hospital reproduction number ($r_0$) is the number of secondary cases during a single admission, while the overall basic reproduction number ($R_0$) combines the number of secondary cases arising from a single admission and the mean number of admissions per patient whilst infectious (1/(1-P)), where P is the probability of an infected individual being readmitted.

For the simulation results in Chapter 3 the value for $r_0$ (within-hospital) was taken from the study by Cooper *et al.* (2003) and set at 1.27. The $R_0$ and P values were determined by the other parameter values used in the model (discharge/admission rates, readmission rate and recovery rate) again taken from a previous study by Cooper *et al.* (2003). These parameter estimates gave a P value of 0.037 and an overall $R_0$ value of 1.32.

Later in the chapter the hospital readmission data is used to estimate P. Using both the recovery rate (as in Chapter 2) and the readmission time distribution (from the data) the percentage of patients likely to be readmitted within the recovery time and therefore of an infected person being readmitted while still infected is

estimated. The value obtained is then compared to the one used for previous nosocomial transmission models and the consequences of any difference seen discussed.

## 5.2 Methods

### 5.2.1 The dataset

A dataset from the UHL NHS Trust described in Chapter 4 (4.2.1) was used for the purposes of this study. The manipulated dataset as described in section 4.2.2 was used for all investigations.

For the study setting of the UHL NHS Trust the relationship between the hospital and community population is that the Trust is the main provider of secondary care for Leicestershire (except for specialties that are not covered in UHL, e.g. neurosurgery and care provided by the two small private hospitals in the area (Nuffield and BUPA)). For patients requiring sub-specialty tertiary care, this is either provided in UHL, or patients are referred as appropriate, e.g. to Harefield for heart/lung transplantation. In addition, the vast majority of admissions to the Trust are from the local population. As the dataset contained 7 years of admission and discharge data for all three hospitals within the Trust, and also as admissions to all three hospitals were from a shared catchment population, not only readmission patterns could be studied, but also how readmissions related to movement within a linked network of hospitals within a near closed system which shared patients.

### 5.2.2 Investigations into readmission patterns

The data were explored and analysed using a number of interrogation techniques in a combination of SPSS (Version 14.0 for Windows), Excel (2003) and MATLAB (Version 7.0). Basic summary statistics and frequency distributions gave an overview of admissions and readmissions to the Trust. Following this, movement between hospitals, times between hospital admissions and length of stay analyses were investigated, again using a combination of summary statistics

to gain information from the data. A brief investigation into the demographics of the 'core group' of patients who are most frequently admitted to hospital was also undertaken.

'Readmission' was defined as any admission by a patient who had a previous admission within the study period, i.e. between April 1st 1998 and the admission in question. As readmissions were estimated retrospectively it was necessary to use only the final 3 years of the total dataset (i.e. from April 2002 to April 2005) for some analyses in order to reduce the effect of left censoring (i.e. admissions occurring before the study period). Furthermore, as readmissions were considered in terms of previous admission, the effects of right censoring could be ignored for the purposes of these investigations. The effects of censoring and precautions taken are explained further in section 5.3.1. For studies that looked at 'readmitted patients' only, these were defined as patients that were admitted more than once during the study period, therefore even on the first admission any patient who *was to be* readmitted was classed as a readmitted patient. Additionally, 'time between admissions' was defined as the time in days between a discharge and following admission.

Investigations into P were performed by determining the percentage of patients (of a particular demographic group) who were readmitted within the recovery time (taken from a negative exponential distribution, mean 370 days). Time in days (at admission) since the previous discharge was taken to be the readmission time.

## 5.3 Results

### 5.3.1 Overall readmission patterns

**Trust Level**

As the data encompassed a 7 year period it was possible for the same patient to be admitted to the Trust more than once. A frequency distribution of the number of times each patient was admitted to the Trust within the 7 years is shown in Figure 5.1. Most patients (51.3%, n=514159) were seen only once and the 75$^{th}$ percentile is at 3 visits. However, the tail of the distribution is considerable with one patient having visited hospital 620 times.

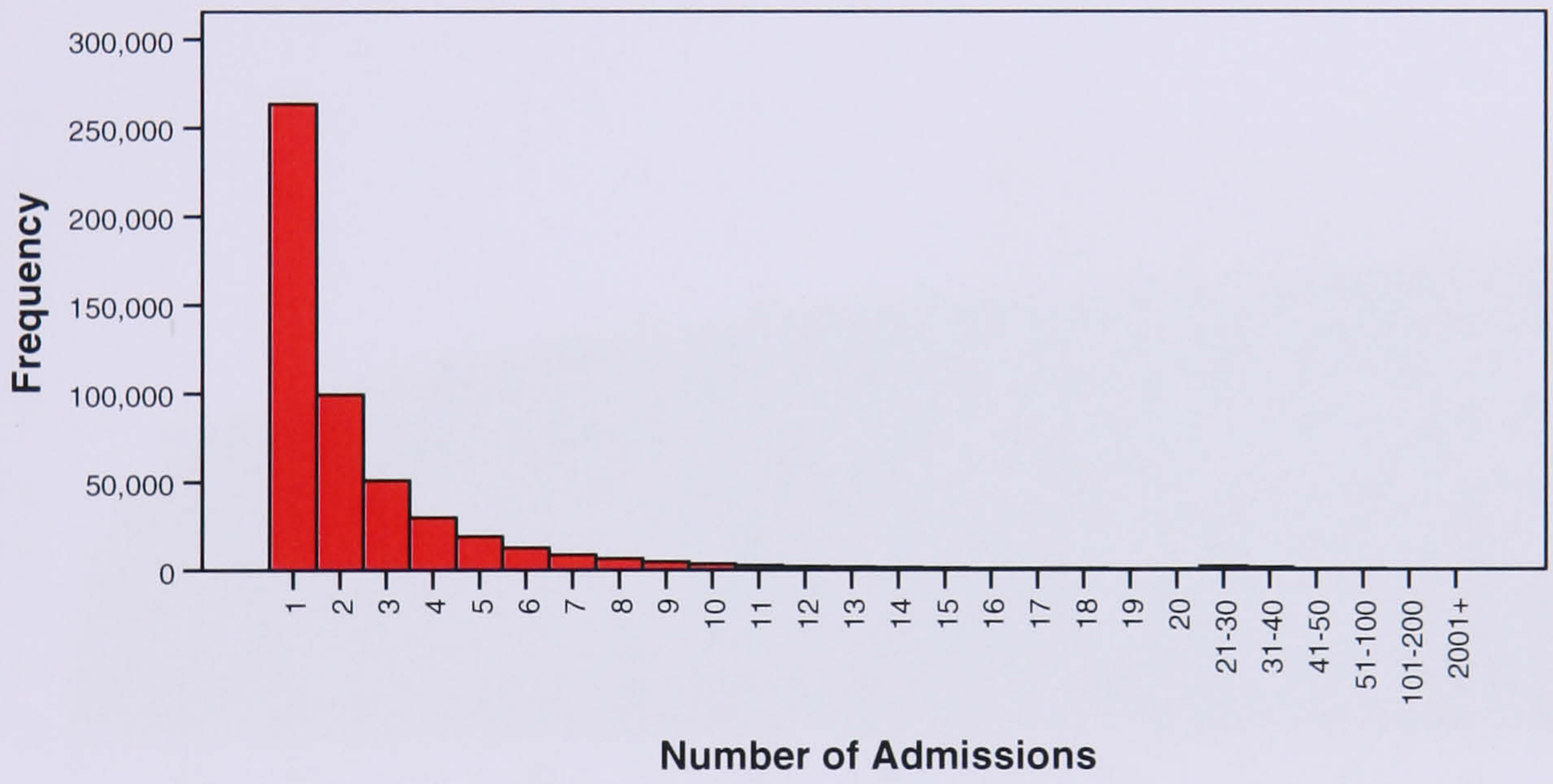



**Figure 5.1** Frequency distribution of the number of times each patient was admitted to hospital, n= 514159 (the total number of patients seen over the 7 year study period).

Patients known to be readmitted accounted for 81.2% (1137799/1401471) of all admissions, with 63.3% of all admissions being readmissions.

**Censoring**

In order to reduce the effect of censoring in the remainder of the readmission analyses a truncated dataset is used. Figure 5.2 was used to determine a cut off point and it was decided that the most accurate estimate of true readmissions

would result from using only the final 3 years of the total dataset (i.e. from April 2002 to April 2005) and looking retrospectively for previous admission. For example, if the whole dataset was used if a patient was admitted 1st March 1998 then again 1st May 1998 the second admission would not be counted as a readmission because 1st March 1998 is before the study period. Whereas if only the final 3 years of the dataset are used there is an increased probability of a readmitted patient having been seen before within the study period and therefore a readmission event would have a reduced probability of being classed as a first time admission. For this reason any analyses that include readmission or hospital visit number the truncated dataset was used. As the proportion of readmissions of all admissions approached a plateau (Figure 5.2) and readmission is estimated in terms of previous admission the effects of censoring could be accounted for.

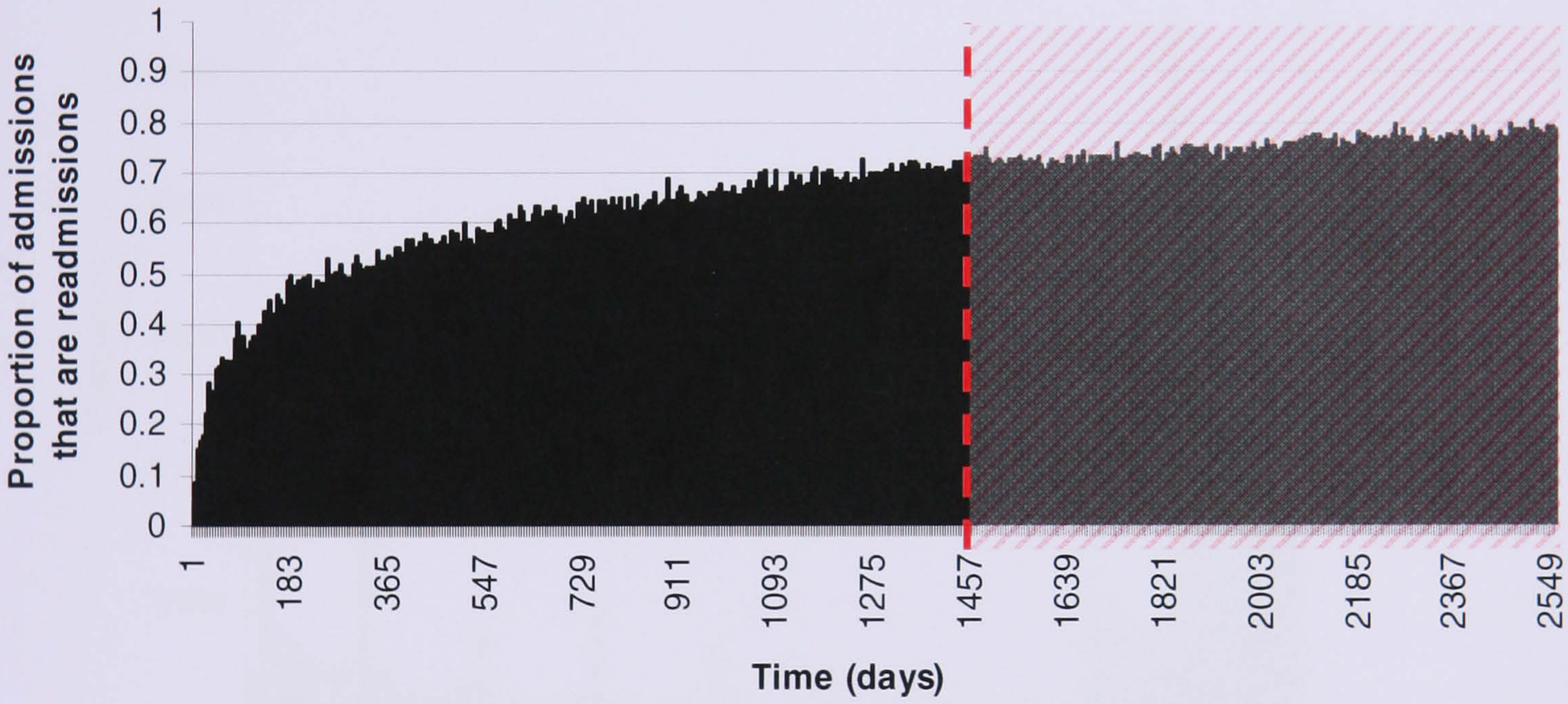



**Figure 5.2** The proportion of admission episodes that are readmissions. The shaded area depicts that chosen for the following analyses, where the proportion of readmissions begins to stabilise.

From April 2002 to April 2005 there were 624338 admissions in total (including both in- and outpatients). Of these 18.3% (114404) were only seen once, 81.7% (509934) were admissions by patients who were readmittees (i.e. either their first visit or a readmission) and 72.4% (451768) were readmissions. In terms of patient numbers, 282913 were seen over the three year period, 40.4% (114404) of whom were seen only once and 59.6% (168509) of whom were readmittees. For

inpatients only, from a total of 291593 admissions, 22.4% (65353) were by patients who were only admitted once over the year study period, and 77.7% (226600) of admissions were by readmittees, with 68.0% (198548) of admissions being readmissions. At a patient level, from a total of 186544 inpatients seen from April 2002 to April 2005, 35.0% (65353) were admitted only once and 65.0% (121191) were readmittees.

The frequency distribution of time between hospital admissions is highly skewed towards shorter time periods between admission episodes. Figure 5.3 shows a generally decreasing distribution; however, when outpatients are included definite spikes can be seen corresponding to readmissions occurring at weekly intervals.

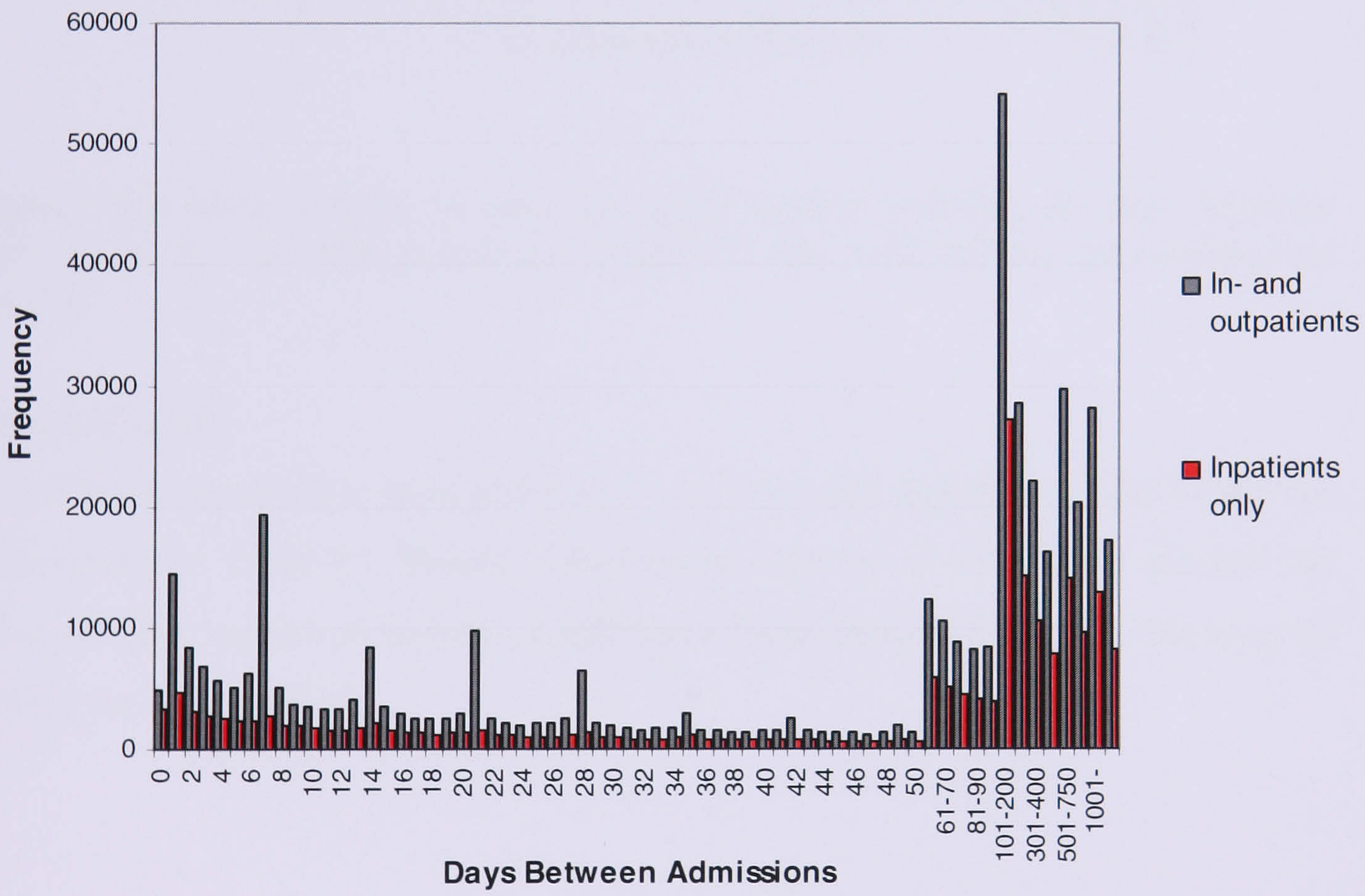



**Figure 5.3** Frequency distribution of days between admissions, for in- and outpatients n=451768, for inpatients only n=198548 (the total number of readmission events from April 2002 to April 2005).

The relationship between time between readmission and length of stay (Figure 5.4) shows that generally longer periods between readmission episodes equates to longer hospital stays.

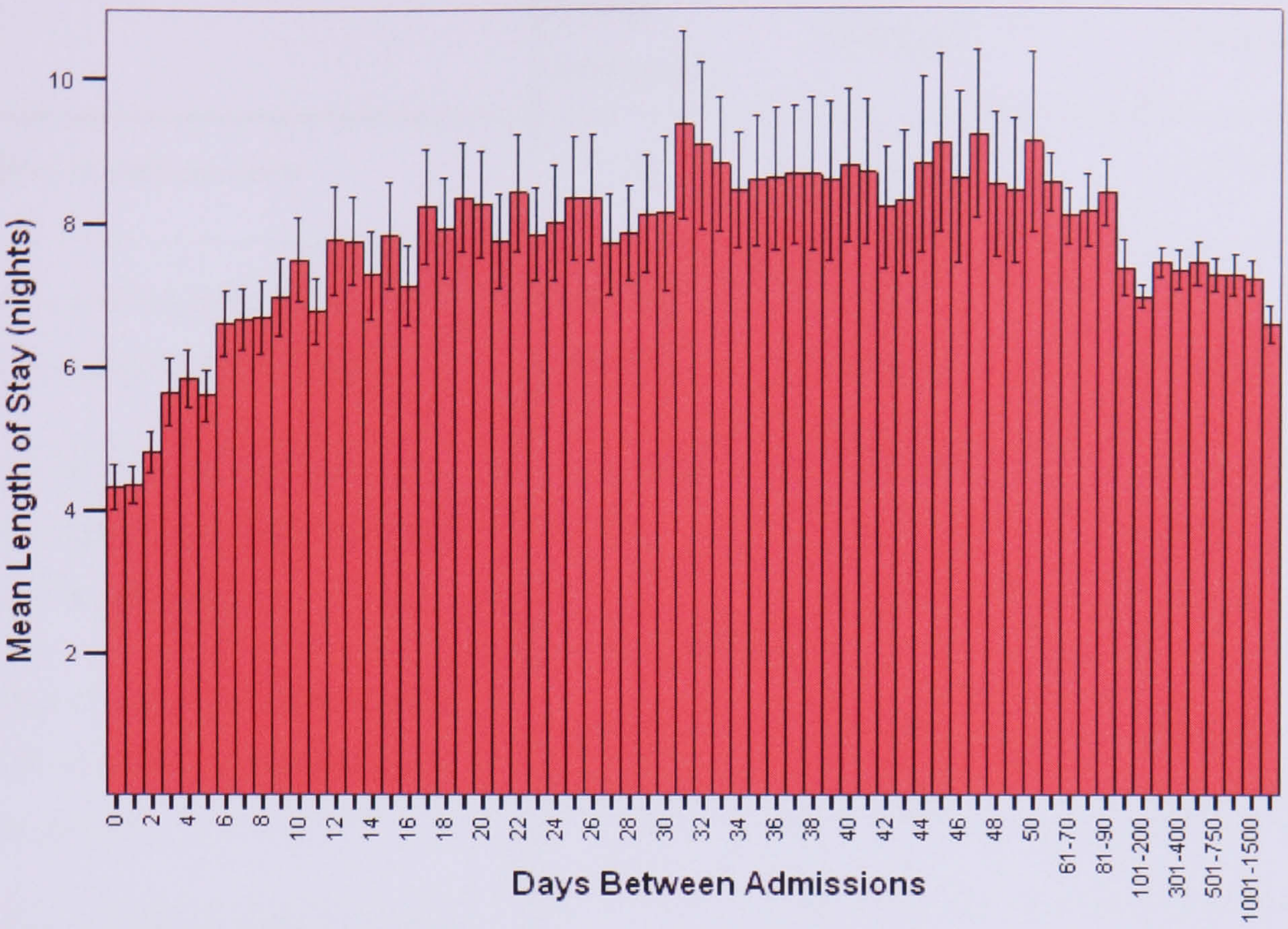



**Figure 5.4** Mean length of stay in nights against number of days between admissions, for in- and outpatients n=887312 (the total number of readmission events).

### Hospital Level

The distribution of patient admissions to each hospital within the Trust's network is described in Table 5.1. Briefly, LRI had the majority of admissions and saw the most patients; moreover patients at LRI were more likely to only visit this hospital during the study period.

| | **Leicester Royal Infirmary** | **Leicester General Hospital** | **Glenfield General Hospital** |
|---|---|---|---|
| Number of patients seen | 333870 | 184244 | 116710 |
| Total number of admissions<br>(% of all admissions to Trust) | 825596<br>(58.9%) | 376341<br>(26.9%) | 199534<br>(14.2%) |
| Mean number of admissions to any hospital per patient (SD); range; 25, 50 and 75 percentiles) | 2.47 (4.7)<br>1-620<br>1 ,1 ,2 | 2.04 (2.4)<br>1-80<br>1, 1, 2 | 1.71 (1.5)<br>1-89<br>1, 1, 2 |
| Number of patients seen only once<br>(as a % of number of patients seen at this hospital) | 191982<br>(57.5%) | 114199<br>(62.0%) | 74290<br>(63.7%) |
| Number of patients seen more than once<br>(as a % of number of patients seen at this hospital) | 141888<br>(42.5%) | 70045<br>(38.0%) | 42420<br>(36.3%) |
| Number of patients who visited this hospital only<br>(as a % of number of patients seen at this hospital) | 241353<br>(72.3%) | 108701<br>(59%) | 59854<br>(51.3%) |
| Number of patients who visited this hospital and one of the other hospitals<br>(as a % of number of patients seen at this hospital) | 76103<br>(22.8%) | 59129<br>(32.1%) | 40442<br>(34.6%) |
| Number of patients who visited this hospital and both others<br>(as a % of number of patients seen at this hospital) | 16414<br>(4.9%) | 16414<br>(8.9%) | 16414<br>(14.1%) |

**Table 5.1** Summary statistics describing admissions to each hospital within the Trust (using full dataset from April 1998 to April 2005).

For each hospital the vast majority of admission events are readmissions with very little difference between hospitals and between in- and outpatients admissions and inpatient admissions (Figure 5.5). In view of this, the remainder of the analyses include both the in- and outpatient populations.

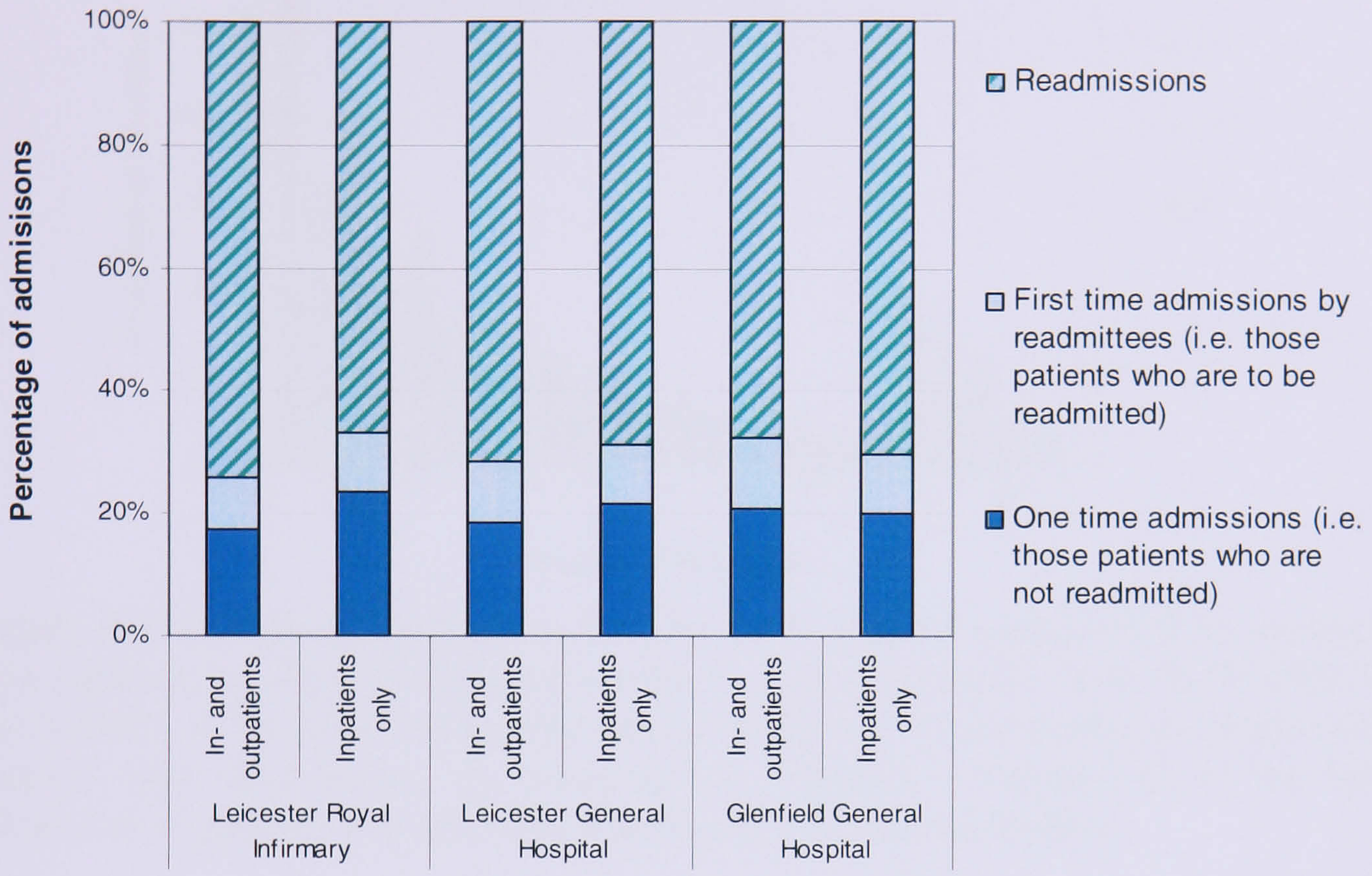



**Figure 5.5** Proportion of admissions and readmissions for each individual hospital for both in- and outpatients and inpatients only (LRI in- and outpatients n=367522, inpatients only n=154083; LGH in- and outpatients n=169459, inpatients only n=87005; GH in- and outpatients n=87357, inpatients only n=50865, all n values correspond to the number of admissions from April 2002 to April 2005).

Figure 5.6 shows at what stage in a patient's readmission history they are likely to visit each hospital. For example, approximately 5% of readmissions to LRI are on a patient's 6$^{th}$ hospital visit. The distribution shows that patient's 1$^{st}$ and 2$^{nd}$ visits to hospital are more likely to be to GH, but as the visit number increases the readmission event is more likely to be to LGH or LRI. For very high visit numbers LRI shows the highest percentage values.

As would be expected, higher hospital admission numbers were also correlated with shorter times between subsequent readmissions (Figure 5.7). For example, the mean number of days between a patient's first and second hospital admission

was found to be nearly 400, whereas this reduces to only about 100 days between a patient's 9th and 10th admission.

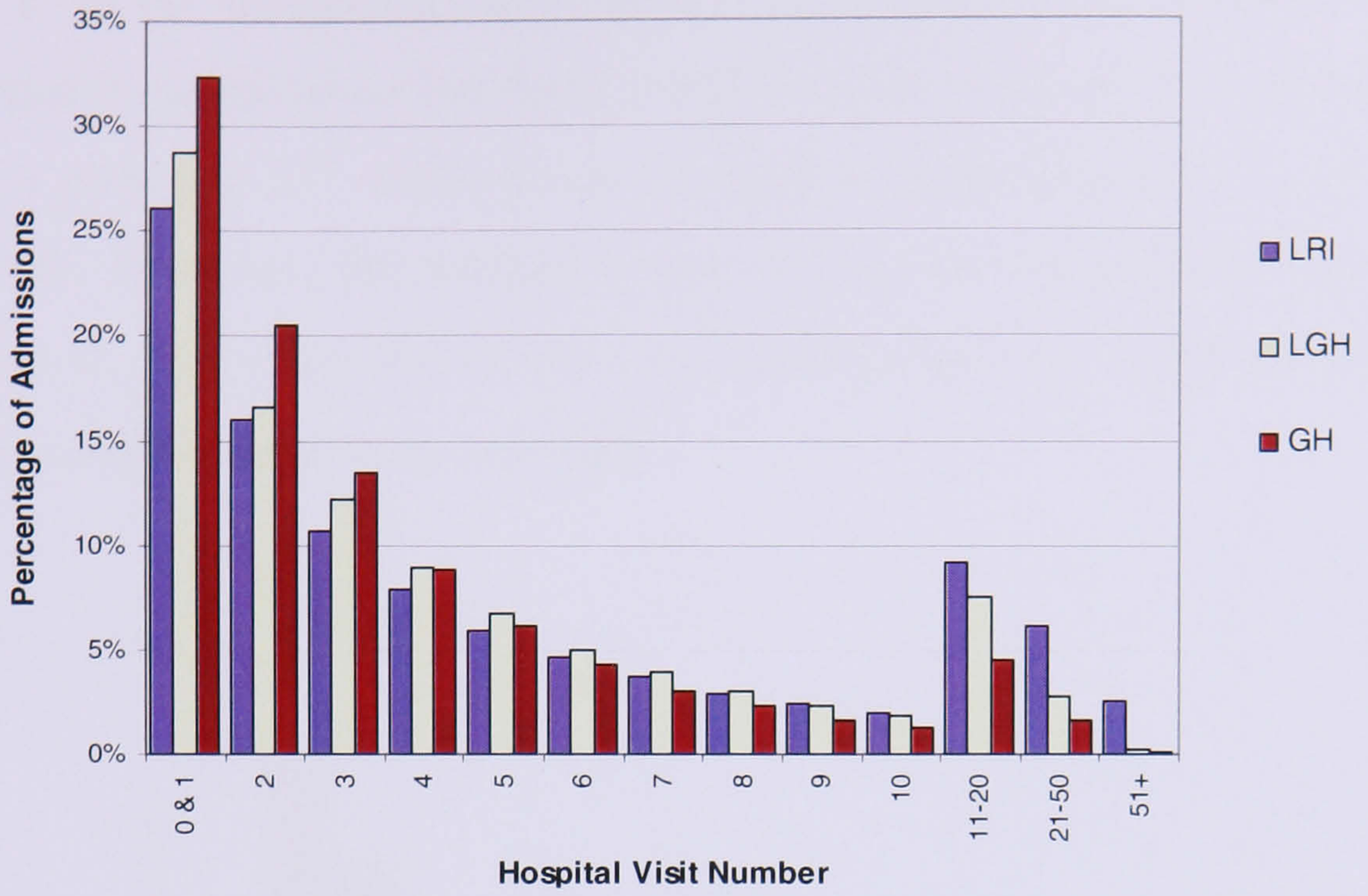



**Figure 5.6** Distribution of admissions to each hospital categorised by hospital visit number, n= 624338 (admissions by in- and outpatients from April 2002 to April 2005). A hospital visit number of 0 corresponds to those patients admitted to hospital only once during the study period, whereas 1 corresponds to the first admission of patients that are to be readmitted (i.e. of readmittees).

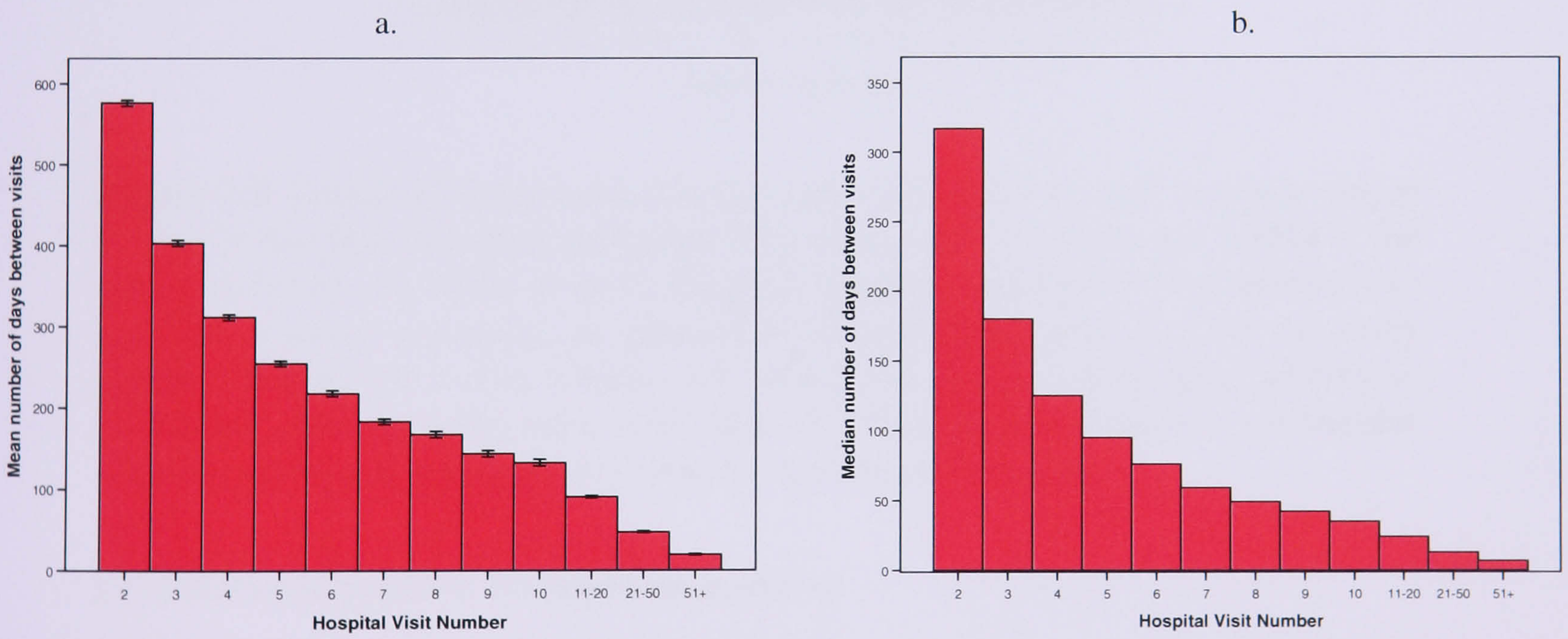



**Figure 5.7** Relationship between hospital admission number and the mean and median number of days since last admission (panels a and b respectively), including 95% confidence intervals (n = 451768, the total number of readmission events from April 2002 to April 2005). For example, the number of days between admissions for hospital admission number 2 corresponds to the time between the first hospital admission and the second hospital admission.

Similarly, length of stay was found to vary according to the number of times the patient had been readmitted to hospital. The mean length of stay in hospital for the patient's 1st to 10th admission can be seen to be between 3 and 4 nights, however, for subsequent readmissions the mean length of stay decreases; the mean length of stay for a patient's 51st readmission or higher, being between 0 and 1 night (Figure 5.8). However, the median length of stay for all hospital visit number groups was 0, except for that of patients with hospital visit number 0-10, where the median length of stay was one night.

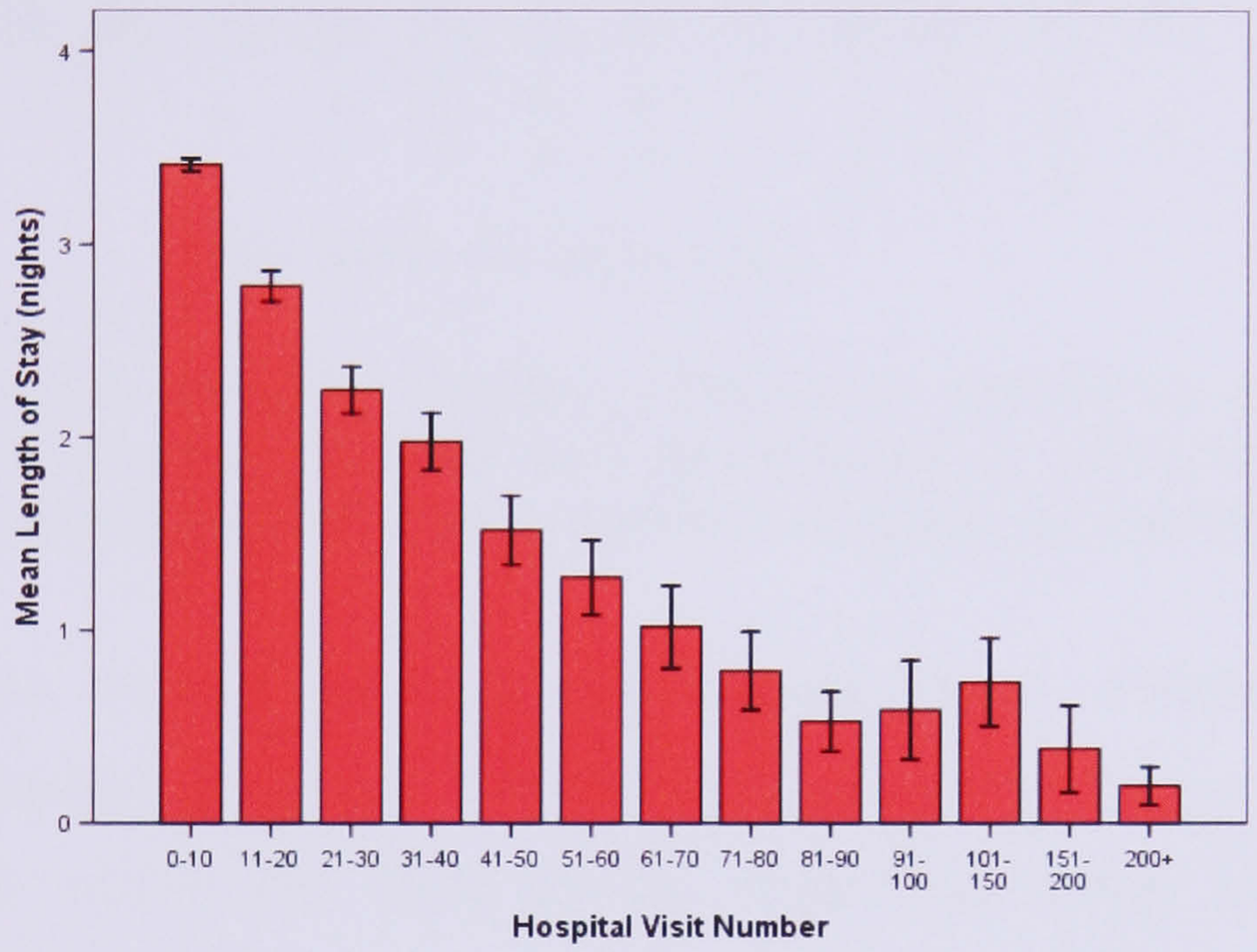



**Figure 5.8** Relationship between hospital admission number and the mean length of stay in hospital in nights, including 95% confidence intervals (n= 1401471 the total number of admission events). Hospital admission number = 0 corresponds to the first hospital admission of patients who were only seen once in the study period, hospital admission number = 1 corresponds to the first hospital admission of patients who are seen more than once in the study period and all subsequent hospital admission numbers correspond to readmission events.

### 5.3.2 Between hospital readmission patterns

Of the 887312 readmissions 79.2% (702847) were to the same hospital as the previous admission and 20.8% (184463) were to a different hospital. However, as time between readmission increases the chances of being readmitted to a different hospital also increases (Figure 5.9).

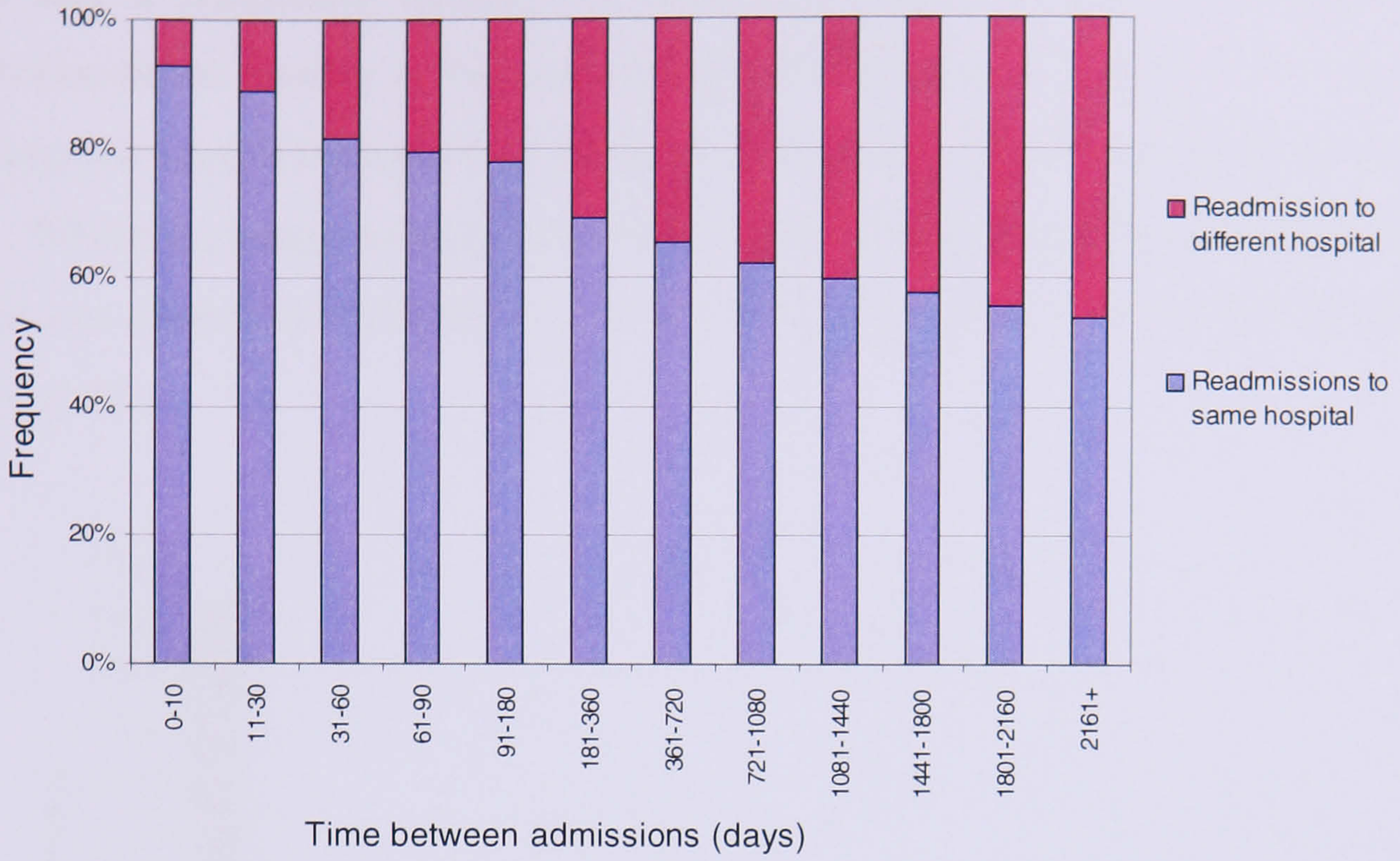



**Figure 5.9** Times between hospital admissions comparing percentages of readmissions to the same hospital and readmissions to different hospitals (n= 887312 the total number of readmission events using the full dataset).

Further analyses into the degree to which patients were 'faithful' to hospitals showed the majority of patients (79.7%) were admitted only one of the Trust's three hospitals within the study period, more than would be expected if readmissions were random, and that only 3.2% admissioned all three (Table 5.2).

| **Number of hospitals visited** | **Percentage of patients expected if readmission was random (from a multinomial distribution)** | **Percentage of patients** |
|---|---|---|
| 1 | 63 | 79.7 |
| 2 | 26 | 17.1 |
| 3 | 11 | 3.2 |

**Table 5.2** Number of hospitals each patient is admitted to, comparing random readmissions between hospitals with the actual readmission distribution from the dataset (n= 514159, the total number of patients seen in the study period).

79.7% of patients (409908) visited one hospital only, 241353 to LRI, 108701 to LGH and 59854 to GH (Table 5.1). The remainder of patients were admitted to

more than one of the three hospitals, with 1276 different permutations of hospital orders and a maximum number of hospital changes of 36. The frequency distribution of the number of hospital changes on readmission (Figure 5.10) shows no change or very few changes of hospital in a string of readmissions to be most likely. Where a change in hospitals did occur on readmission the most common change was either from hospital 1 to 2 (i.e. LRI to LGH) or 2 to 1 (LGH to LRI) (Figure 5.11).

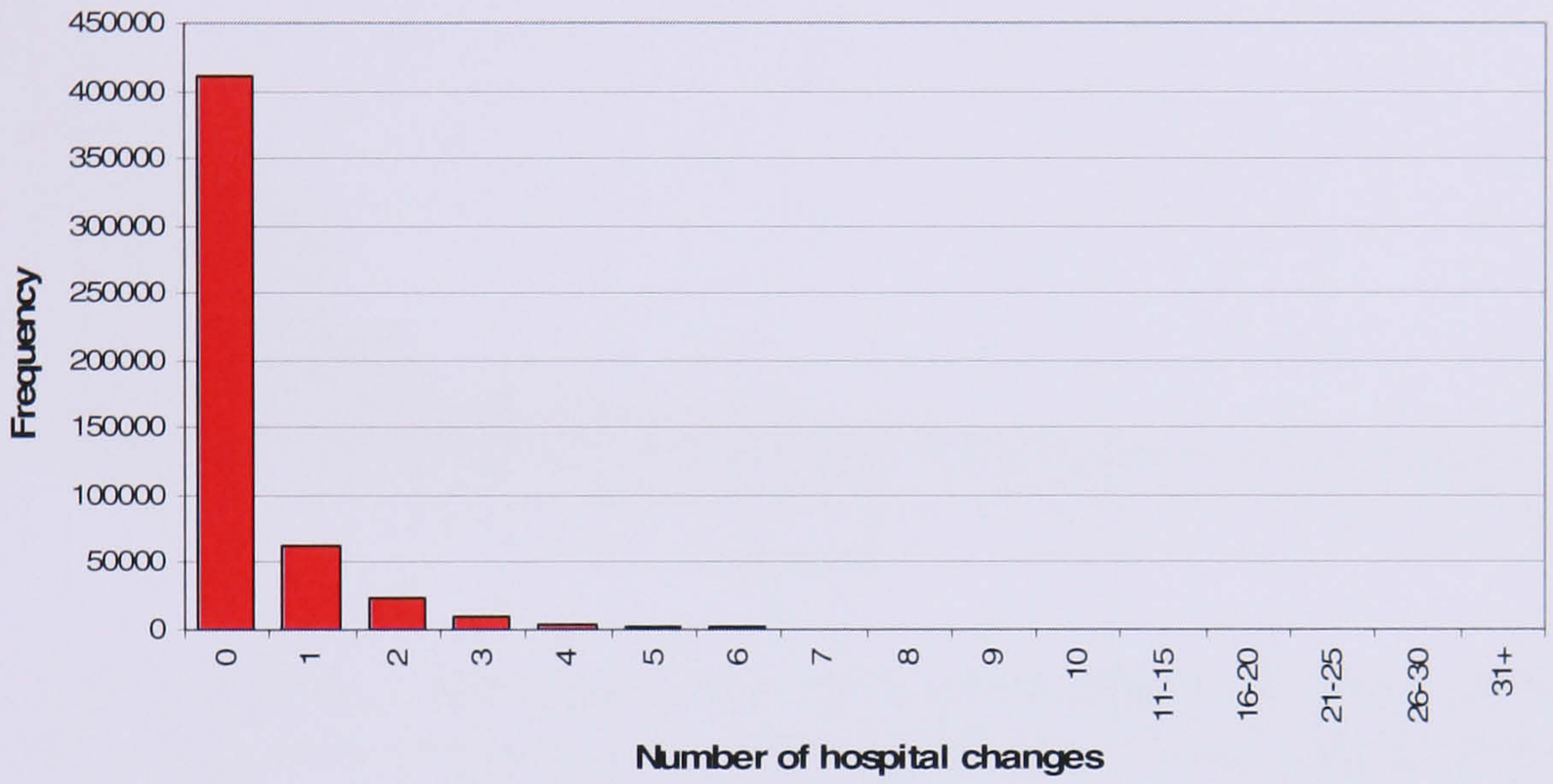



**Figure 5.10** Frequency distribution of number of changes in hospital during string of readmissions, 0 changes correspond to patients who visited only one hospital (n= 514159, corresponding to the full dataset).


**Figure 5.11** Frequency distribution for each permutation of order of hospitals visited (including only permutations that applied to at least 200 patients where there was at least one change of hospital between visits, n= 95633 patients, taken from the full dataset). 1 = Leicester Royal Infirmary, 2 = Leicester General Hospital, 3 = Glenfield General Hospital.

The percentage of admissions to each hospital based on hospital of discharge (Table 5.3) reinforces the finding that the majority of admissions are to the hospital of previous discharge. Further to this, it is the symmetry in hospital changes that is most striking. Effectively this symmetry means that changes within certain hospital pairings are more likely with movements in either direction within the pair being approximately equal. Namely, changes between LRI and LGH are most likely, followed by LRI and GH, and lastly LGH and GH.

| | | Previous discharge | | |
|---|---|---|---|---|
| | | **1 (LRI)** | **2(LGH)** | **3(GH)** |
| **Next admission** | **1(LRI)** | 52.1% | 5.2% | 3.5% |
| | **2(LGH)** | 5.0% | 19.4% | 1.7% |
| | **3(GH)** | 3.6% | 1.8% | 7.8% |

**Table 5.3** The percentage of admissions to any of the three hospitals given discharge from any of the three hospitals (n=887312 the total number of readmission events).

### 5.3.3 Readmission patterns for different demographic groups

On comparison of age for different patient groups (based on how many times they are admitted) it was found that patients who were readmitted at least once were more likely to be either young adults (between 25 and 35 years), or elderly (at least 70 years old). Furthermore, patients who were readmitted the most (at least 20 times) were most likely to be older (approximately between 50 and 80 years). Basic summary statistics are shown in Table 5.4.

| | **Patients who were admitted only once during study period (n= 263585)** | **Patients who were readmitted at least once (≥1) (n= 1137767)** | **Patients who were admitted to hospital at least 20 times (n= 71352)** |
|---|---|---|---|
| Mean | 34.56 | 47.51 | 50.81 |
| Median | 33 | 49 | 55 |
| Mode | 0 | 0 | 68 |
| Range | 0-107 | 0-109 | 0-96 |

**Table 5.4** Summary statistics showing ages of patients (in years) in different groups, based on the number of readmissions.

Patients who are admitted less than 30 times were more likely to be female, but those patients who were admitted more than this were more likely to be male (Figure 5.12).

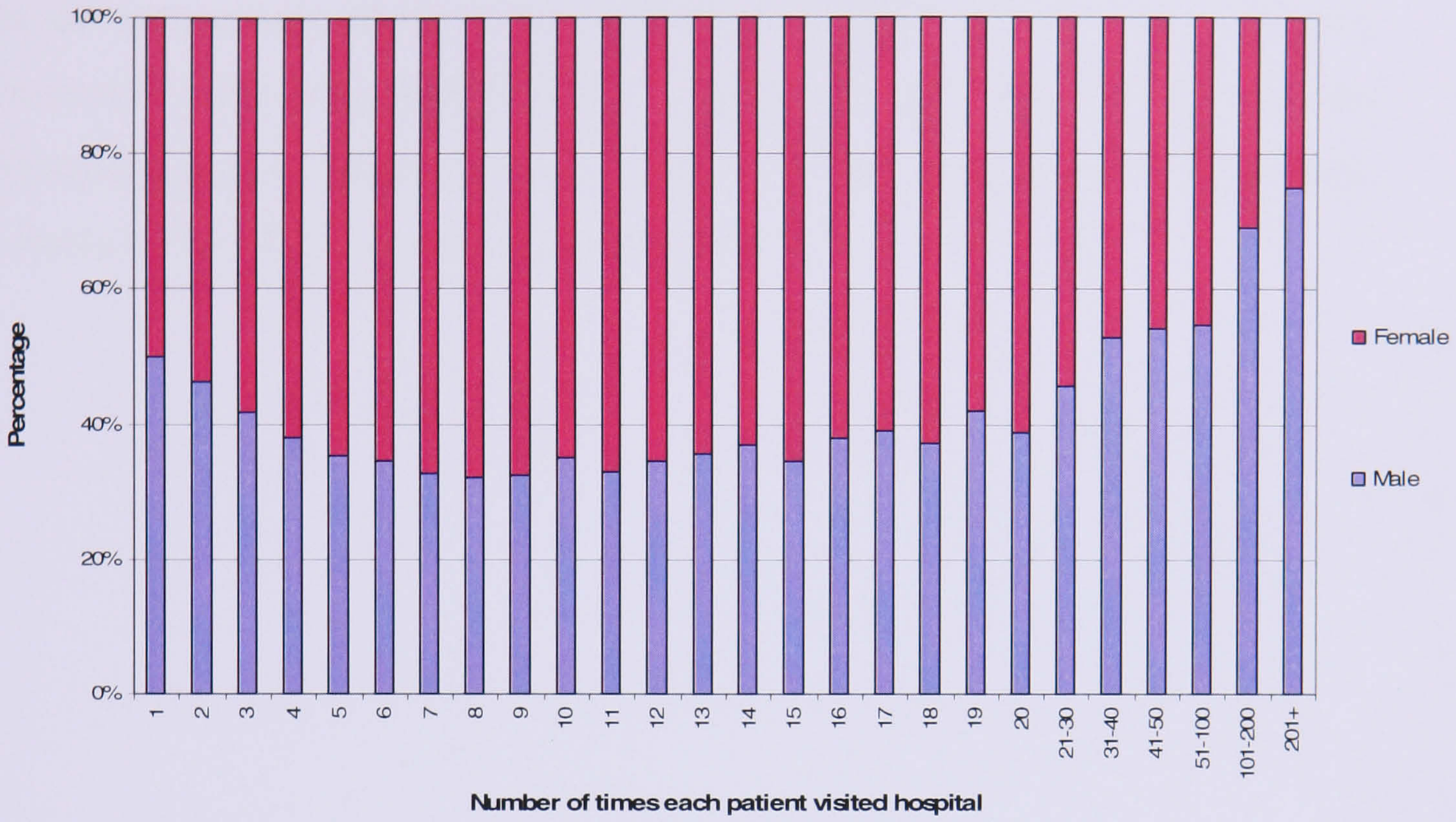



**Figure 5.12** Number of times patients visit hospital (n= 514149 the number of patients that were seen in the Trust from April 1998 to April 2005) split by gender. For example, of all the patients who visited hospital 20 times 38.7% were male and 61.3% were female.

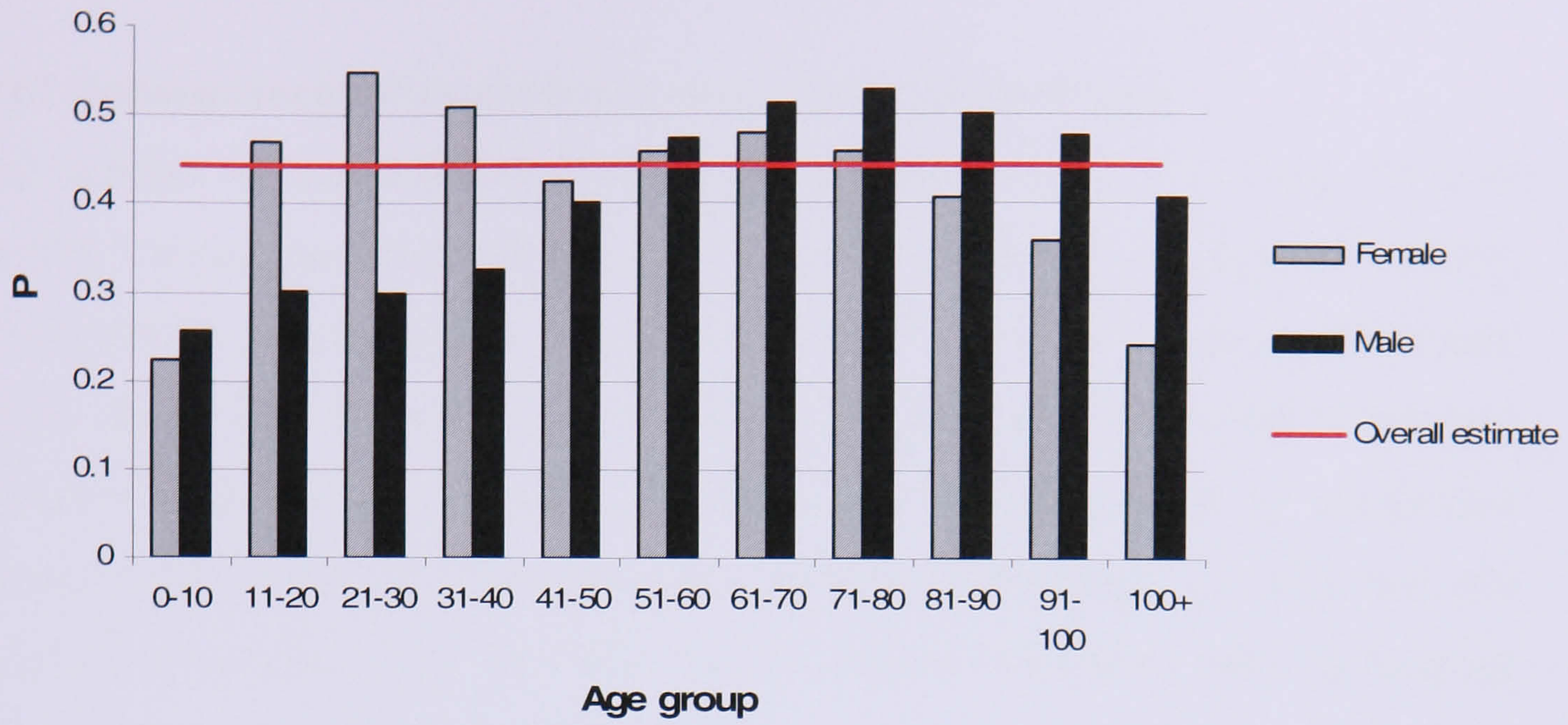
### 5.3.4 P-value estimation

The probability of an infected patient being discharged and readmitted while still infected (P), was estimated from the dataset assuming a negative exponential distribution of loss of infection over time with a recovery rate of 0.0027/day (mean recovery time of 370 days). The mean P value of all patients was calculated to be 0.442, i.e. 44.2% of infectious discharges are readmitted while still infected. This P value gives an estimate of the mean number of admissions whilst infected (1/(1-P)), as 1.79. Excluding day cases this value dropped to 39.8%, i.e. a mean number of admissions of 1.66.

Figure 5.13 explores P with respect to age and gender; it is found that for younger patients (less than 50 years) it is the females who have a greater chance of being

readmitted within the recovery time. Females in the 20-30 year age category seem to pose particularly high risk with 54.5% of admissions by this group being followed up with a readmission episode within a mean of 370 days (the recovery period). Conversely, for patients over 50 years, as age increases it is the males who are increasingly likely to be readmitted. Overall, females have a slightly increased P value compared to males (0.46 compared to 0.42 respectively, this difference is further enhanced on the exclusion of day cases where P for females increases to 0.53 and for males drops to 0.36).

a.




b.

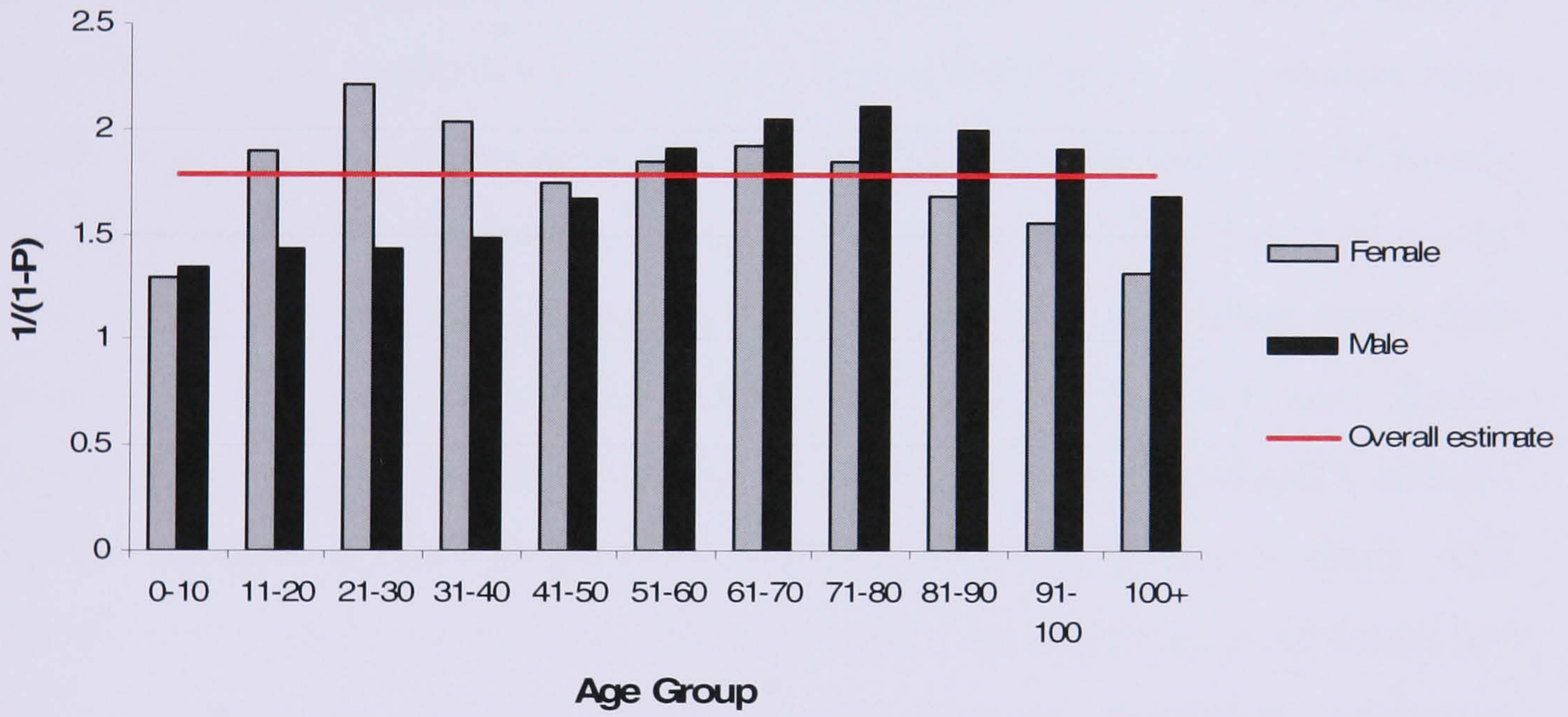



**Figure 5.13** Heterogeneities in readmission rates with respect to age and gender, panel a) shows P values, the probability of an infected individual being discharged and readmitted while still infected, panel b) shows 1/(1-P) the expected number of admissions while infectious. Results are shown for different age groups split by gender, n= 887275.

## 5.4 Discussion

### 5.4.1 Consequences of readmission patterns for transmission

The number of hospital visits was generally low (Figure 5.1), with 75% of patients visiting the Trust 3 or fewer times over the 7 year study period. However a few patients visited the Trust repeatedly over the 7 years, up to nearly 100 times a year, and it is these readmission events that make up the majority of hospital episodes. Basic statistics, such as 81.2% of all admissions are by readmitted patients and 51.3% of all patients are readmitted, highlight the fact that the majority of hospital days are taken up by patients who have been in hospital before or are to come in hospital again.

In terms of transmission this pattern can work in two ways. Firstly, a high rate of readmission means a greater probability of reintroduction of infection, especially given the fact that readmission events are more likely to be over shorter time periods (Figure 5.3) and thus the shorter the duration of infectiousness necessary for readmissions to be in infection threat. However, the strong presence of a core group, of frequently readmitted patients, within the hospital population means that transmission is mostly contained within that group i.e. they are mostly transmitting to each other (either directly or indirectly). An individual's contact rate with members of the core group, in which a higher prevalence is likely, will determine their risk of acquisition. These dynamics are similar to those found for sexually transmitted diseases where sexual partner networks determine transmission patterns. Ghani *et al.* (1996) suggest that distinguishing between the role of contacts in risk of acquisition and the risk of transmission may be significant. In a further study Ghani and Garnett (2000) describe how an individual's risk of acquisition depends not only on their contacts, but also on the contacts of their contacts, as well as the prevalence within the associated networks; whereas, risk of transmitting infection depends more on individual behaviour.

Most readmissions (79.2%) were to the same hospital from which discharge occurred, with the vast majority of patients (79.7%) only admissioning 1 out of the 3 hospitals within the Trust (Table 5.2). This pattern has two main implications in terms of transmission.

Firstly, there is a relatively low chance (0.208) that an infected patient discharged from one hospital will be readmitted to another hospital, and an even lower chance of doing so while they are still infected, especially on consideration of the fact that readmission episodes to a different hospital were associated with longer periods of time between one admission and the next (Figure 5.9), presumably admissions associated with different diseases/ailments. Therefore there is a relatively low chance of patients becoming infected with MRSA in one hospital and subsequently spreading it to another hospital. In effect, 'core groups' appear to be largely hospital-specific and so have the potential to contain infection within individual hospitals, meaning that epidemic behaviour in one hospital may not necessarily generate epidemic behaviour in neighbouring hospitals.

Secondly, the chance of an infected patient being discharged and readmitted to the same hospital is relatively high and it is this kind of patient movement pattern that leads to persistence (either through re-seeding or 'fuelling' an existing epidemic). For example, if an epidemic were to occur within a hospital and an infected patient discharged, then in the time between their discharge and readmission the epidemic may have been controlled. Thus a susceptible population is created, meaning that upon readmission the individual would have the potential to 're-ignite' the epidemic.

This effect of reintroducing infection to the hospital of discharge may be enhanced due to the finding that patients who were readmitted most quickly, i.e. in the shortest time since their last discharge, were even more likely to return to the same hospital from which they were discharged (Figure 5.9). Moreover, those that were most quickly readmitted were also found to have been in hospital many times previously (Figure 5.7). This high number of same-hospital admissions

within a small time frame makes these patients ideal vectors for infection: they are at an increased chance of acquiring infection due to their numerous hospital visits and have an increased chance of transmitting infection due to 'quick' readmissions i.e. before recovery. However, it was also found that for higher hospital admission numbers shorter hospital stays were more likely (Figure 5.8). Therefore, due to length of stay being a proven risk factor for nosocomial infections (Graffunder and Venezia, 2002; Safdar and Maki, 2002), the chance of either becoming infected or infecting others may be reduced. In addition, longer stays in hospital were associated with longer times between visits, again having the potential to reduce the threat of reintroduction of infection.

Further work would need to be undertaken to determine the degree of between hospital movement that would ensure each hospital reaches a high prevalence as well as being able to seed others.

**Heterogeneities in readmission**

Not all hospitals within the Trust share the same readmission patterns. For example, LRI had the highest proportion of readmissions (Figure 5.5) and from Figure 5.6 it can be seen that these readmissions correspond to higher hospital visit numbers. However, LGH and GH were associated with those patients who had only been readmitted a few times (i.e. lower hospital visit numbers). Again, hospitals associated with short stays (LRI) (Figure 4.9) were also associated with more frequent visits from patients (Figure 5.6) and similarly the hospitals associated with longer hospital stays (GH) are associated with less frequent visits.

These patterns imply that certain hospitals have a higher epidemic risk than others. Namely, those at which the readmittees have been into hospital most times previously (and therefore have an increased probability of being either infected or colonized by MRSA) and those whose patients are readmitted most frequently.

As well as variations between hospitals, different demographic groups were also found to have differences in readmission patterns; most notably young women

(21-30 years) and also elderly males appear to be 'core groups'. Analysis reveals that women in reproductively active age-groups are amongst the most likely people to be readmitted to hospital whilst still infected, and consequently the group most likely to have a high prevalence of HCAI. A HCAI epidemic in reproductively active women may not have occurred previously for three reasons. First, this group is less frequently exposed to antibiotics. Second, Obstetrics & Gynaecology is relatively separate from others in terms of patient placement within hospital and staff cross-over. Third, the length of stay (LOS) of patients admitted to this specialty is shorter (mean LOS 1.04 nights for obstetrics, 1.21 nights for gynaecology compared to 6.61 nights for females in all specialties (results from chapter 4, section B)). However, should a HCAI enter this group it is likely to become well established at a high prevalence, therefore special attention should perhaps be given to ensure this does not occur.

**Infected readmission estimates**

Overall, it was found that approximately 44.2% of infected discharges will subsequently be readmitted to the Trust (either to the same or different hospital from which discharge occurred) within the recovery time i.e. while they are still infected and infectious. This is a much higher parameter estimate for P than that used in the previous models by Cooper et *al.* (2003; 2004a) and that used in Chapter 3. The previous estimates gave a P value of 0.037, giving approximately half the number of infected admissions per infected patient to that estimated using these findings (1.04 compared to 1.79).

Despite these estimates being calculated from a single dataset, the fact that they are so much higher than previous estimates, with almost half of the infected discharges being subsequently readmitted, highlights the need for more collection and analysis of such data.

It must be remembered that the accuracy of all readmission pattern analyses is compromised due to the effects of censoring. There may be some value in developing a model of admission behaviour, in order to reduce bias brought about

by censoring. No such model has been developed here, but would be a sensible next step in the investigation of readmissions.

### 5.4.2 Consequences of readmission patterns for infection control

The determination of a 'core group', and more importantly identification of its members, would have obvious benefits for infection control. It is these few patients who are admitted frequently, who are likely to have most contacts and take up the majority of patient days, who are of most interest from an infection control perspective. If these patients were to have an infectious disease then without effective surveillance they would provide a source of infection upon each visit. However, if frequent readmittees were 'flagged' in some way then the threat posed by them could be reduced as they would be known to be high risk upon admission and therefore could be treated accordingly.

The fact that readmission events are generally more likely to be over shorter time periods (Figure 5.3) even further highlights the need for effective surveillance of readmittees. Furthermore, the potentially predictable nature of some readmissions, for example the weekly readmission patterns seen within the outpatient population (Figure 5.3), could be made use of when devising a surveillance strategy. In general, knowledge of both patient length of stay and how frequently they visit hospital may determine whether or not a particular control strategy will succeed or fail, and should therefore be considered during design.

Parallels may be drawn between targeting control to frequent hospital readmittees and that explored by Sutton *et al.* (2006) where persistent offenders were vaccinated against hepatitis B at prison reception, a strategy aiming to increase coverage of the high risk injecting drug user population.

The faithfulness of patients to hospitals is also potentially advantageous for infection control in that faithfulness effectively constrains transmission within particular hospital populations, thus reducing spread to other hospitals within the network. Effectively, clustering of the patient population is generated. However,

despite the low probability, there is still a chance of infection transfer occurring and therefore must not be overlooked in infection control practices, particularly when the transfer of infection maybe into a susceptible population (i.e. a hospital without an epidemic) and thus being a perfect setting for effective transmission. For example, Scanvic *et al.* (2001) find a high percentage of their MRSA cases to be due to transmissions from outside hospitals.

Heterogeneities in readmission, by hospital and demography, further our understanding of the frequently readmitted 'core group'. An increased knowledge of these patients would be of great benefit in terms of infection control, as these are the patients with the greatest potential to become infected and reintroduce infection on each visit. In addition, this is the patient group likely to have the highest prevalence, due to the predominantly within-group transmission. Therefore any control strategy that targeted the demographic groups/hospitals most likely to be in the 'core group' would be likely to have the greatest influence on overall infection levels, both in the short term (i.e. for the 'core group' itself) and the long term (by reducing the probability of transmission to individuals outside the group and reducing the probability of reintroduction of infection).

Analysis of heterogeneities in readmission rates provide insight into those patients who may need to be prioritised within infection control policies and although difficult to conceive of practically, overall, any method of reducing P would be likely to be an effective intervention strategy.

The fact the probability of readmission of an infected individual, whose infection was acquired on a previous hospital admission and to whom recovery has not yet occurred, is so much higher than previous estimates implies that reintroduction of infection may be a critical factor in the transmission dynamics of MRSA. The identification of factors of influence to transmission allows the development of more informed control strategies; as discussed in earlier chapters a higher P value and a setting of greater patient movement (particularly infectious patient movement) between the hospital and community populations will have an impact

on infection control strategy success. Due to their influence on transmission, and therefore on control strategy success, readmitted patients (especially those readmitted within a year) should be an infection control priority and there may be value in strategies such as screening on discharge or screening and isolating on admission. Moreover, the analytical results in Chapter 2 find that increases to the value of P relate to an increased benefit in on-admission screening. Therefore, the fact that our estimated P value is much higher than previously estimated implies a strategy solely comprised of random screening may not be the preferential strategy. Indeed, the greatest control at P=0.45 (Figure 2.3) find an approximately 50% random screening to 50% on-admission screening to be optimal. Therefore a strategy that is tailored towards the targeting of readmittees may be of greatest value.

Further mathematical modelling studies into the effectiveness of infection control strategies given much higher, and therefore, according to these findings, more realistic, readmission rates are shown in Chapter 6.

### 5.4.3 Conclusions

These findings provide the first direct estimates of the impact of readmission and heterogeneities in readmission rates. The results shown imply readmissions may have a definite influence on nosocomial infection transmission dynamics, with transmissions caused by patients admitted from the community potentially being of more importance than within-hospital transmission. This shift from hospital driven to admission driven transmission dynamics would likely provide very different transmission patterns and further work in this area would need to be undertaken to ascertain the effect this change in focus would have on infection control strategy advice.

Clear representation and increased knowledge of these kinds of statistics could help infection control practices within hospitals greatly. Using these patterns and distributions to determine a realistic setting, various control strategies may be devised and tested using mathematical modelling. Further work in this area needs

to be undertaken to link such findings on patient demography and patient flow to the development of a comprehensive model of a hospital system. Such a model would enable theoretical testing of control strategies within a particular hospital network, in this case for the UHL NHS Trust. Additionally, such models could be generalised and be useful in many areas, not only for epidemiology and infection control but also for areas such as hospital management and planning. Such a model has not been developed here since the observed data will be used in future chapters.

# Chapter 6

# Using hospital data to inform model development in order to further understand transmission dynamics of healthcare-associated infections

The purpose of this chapter is to describe how the mixing patterns and hospital demographics obtained from the hospital data were used to inform a mathematical model. The development of a stochastic model of infection transmission within a setting of real patient movements between hospital and community is described. Namely, real patient movements in and out of the UHL NHS Trust are simulated. The model simulates this setting for a period of 7 years from 1998 to 2005, where all admission and discharge events are as those described in Chapters 4 and 5. To the author's knowledge, this is the first time such a model, using real patient movements around a healthcare network, has been developed and used to further understanding of HCAI transmission dynamics. Simulation results, showing epidemic behaviour and preliminary investigations of control strategies in this setting are given in terms of numbers of infected patients over time.

## 6.1 Introduction

One of the most significant findings from Chapter 5, especially from an infection control point of view, was that the majority of patients in hospital are those who

have been in hospital before (with approximately 80% of readmissions occurring within a year of discharge). Overall, readmissions were found to be much more common than previously thought with the mean number of infected admissions estimated to be almost double that of previous estimates. The elderly, especially males, and young females (21-30yrs) were found to have a particularly high risk of readmission within a short time frame.

From these results it is clear that the model developed in Chapters 2 and 3 simulates infection in a different setting to that described in the data. In these simulations readmission was much less likely and therefore the effect of reintroduction of infection may have been underestimated. Moreover, the analytical results in Chapter 2 indicate that movement patterns may be key to infection control strategy success or failure, in settings of different patient movement patterns different control strategies may be appropriate. For example, whereas within-hospital screening may be beneficial in a setting of low patient readmission, as readmission rates increase the benefit of this strategy may decrease and the benefit of on-admission screening increase. As discussed in Chapter 5, this dependence of control strategy success on patient movement patterns, coupled with the finding that readmissions are much more common than previously thought, suggests that in a more realistic setting (with higher readmission rates) the control strategy of most benefit may be different to the results seen in Chapter 3. Therefore a more realistic representation of the hospital setting in terms of patient movements will aid in understanding the best strategy to be adopted.

Creating a model using real patient movement patterns over a defined time period will have two major outcomes: firstly, a more realistic model will provide greater insight into HCAI transmission dynamics generally and secondly, despite not being attempted here, these types of models could be used to provide quantitative control strategy advice to the hospital(s) to which the data applies.

In order to simulate the situation at UHL NHS Trust more closely a distinction is made between the three different hospitals within the Trust, rather than treating all three hospitals as one entity. The development of the original model to include three hospitals and a community is described. The mixing and readmission patterns obtained from the individual hospital data analyses will be used to inform the model framework, such that a multi-centre model with non-random mixing is created. This is the first attempt at developing a multi-centre model using real patient movements within the network and will have the benefit of allowing investigation of transmission in a heterogeneous setting.

## 6.2 Model Development

### 6.2.1 Single-centre model

An individual-based model (IBM) was developed such that the infection status of each individual was recorded over time. The model was developed to follow closely the theoretical, stochastic model described in Chapter 2.

A closed hospital and community population was modelled. As described in Chapter 5 (5.2.1) the majority of the community population uses the Trust and the majority of the patients in the Trust are from the community population; therefore the assumption of a closed hospital and community system seems a reasonable one for this particular setting. Patient movements between the hospital and community were modelled on an individual level. Patients moving into hospital acquired the status 'ins' and patients moving out 'outs'. Once admitted, 'ins' were given the status 'inpatient' (which was then subsequently lost upon discharge). Admissions and discharges were carried out on a daily basis with the assumption that admissions and discharges occur simultaneously. In this way, day cases are never considered a part of the inpatient population and are therefore effectively excluded. For MRSA this assumption seems reasonable as the major infection threat will come from inpatients.

It is important to note that admissions and discharges were simulated exactly as they occurred in real time; therefore these events were not modelled stochastically and did not have associated estimated parameters, due to this there existed only one community group. This differs from the model described in Chapter 2 where two community groups existed, each associated with a different readmission rate.

Infection was included as a stochastic event such that each individual also had an infection status. For all simulations it was assumed that initially there existed 100 infected individuals within the community population (chosen at random initially, but constant between runs). Infection (or colonization) of a susceptible patient lead to a status change from 'susceptible' to 'infected', these patients were assumed infectious and able to infect other susceptible individuals until loss of 'infected' status upon recovery. Upon discharge, infected patients retained their 'infected' status within the community population, and were assumed to recover at the same rate as infected individuals within the hospital.

The addition of an infection control strategy including patient screening and isolation was created using further categorisations. Screening allowed detection of infected individuals; this detection being accompanied by the addition of a 'detected' status. Again screening and detection occurred either within the hospital (random screening), on patient admission (on-admission), or alternatively was comprised of a combination of the two. Screening was carried out stochastically, but the method used differed slightly from that in Chapter 3. Here, the number of people screened per day was chosen, thus establishing effort, and the value of an additional parameter $\sigma$ (taken from a range of 0-1, where 0 = solely on-admission screening and 1 = solely random screening) determined which strategy was adopted. It is worth noting that recovery of a detected individual did not cause loss of their 'detected' status. This model could therefore be developed to explore the effect of re-screening previously detected patients. However, loss of 'detected' status did occur on hospital discharge. Therefore it was possible for an infectious patient to be readmitted to hospital and their infection status unknown upon admission, despite being known during their

previous hospital stay. Another extension of this model would therefore be to explore the possibility of targeting screening to those individuals who were known to be infected during their previous hospital visit, especially if this was in the last year, for example. The inclusion of a fixed capacity isolation ward allowed detected individuals to be isolated while capacity allowed. Upon isolation the individual gained the additional status of 'isolated', which was lost upon patient discharge or patient recovery. A diagram depicting the model's structure is given in Figure 6.1 and the parameter values, stochastic events and their corresponding rates in Tables 6.1 and 6.2.

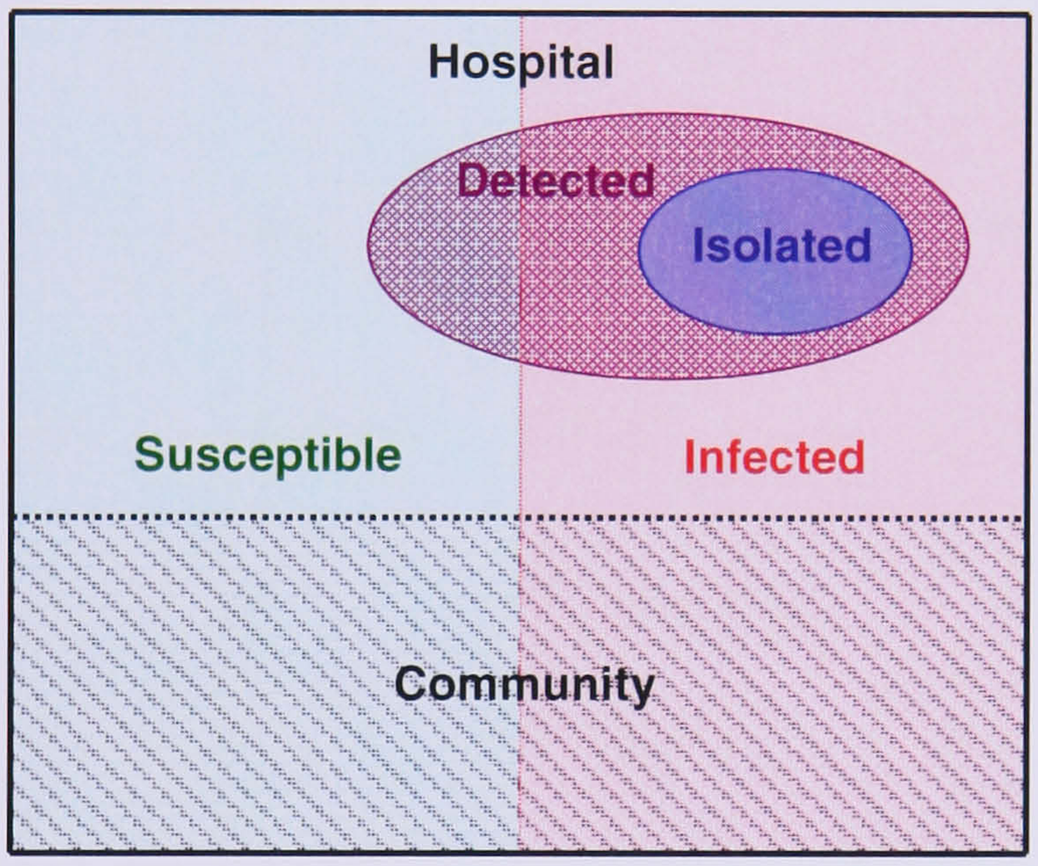



**Figure 6.1** A Venn diagram representing the entire study population in terms of status possibilities, where each set represents a status type. For example, the detected patient group is largely made up of infected patients, some of whom may also be isolated, but is also partly made up of susceptible patients; all detected patients are part of the hospital population.

| Parameter | Symbol | Value | Reference |
|---|---|---|---|
| Transmission coefficient | $\beta$ | 0.1622 (unless otherwise stated, where values of 0.1126 and 0.1939 are used) | As in chapter 2 (as described in section 6.2.1) |
| Recovery rate (day $^{-1}$) | $\gamma$ | 0.0027 | As in chapter 2 |
| Isolation ward capacity | NISO | 20 | - |
| Average number admissions/ day | NA | 548 | From dataset (as described in chapters 4 and 5) |
| Average number in hospital/ day | NH | 1719 | From dataset |
| Overall population size | NH+NC | 514159 | From dataset |
| Screening effort | $\varepsilon$ | Range: 0-NA | - |
| Screening type | $\sigma$ | Range: 0-1 | - |

**Table 6.1** Parameter values used in the 'real-movements' models

| Event description | Event Rate |
|---|---|
| Infection of a susceptible within the hospital | $\beta \cdot \frac{\sum(\text{susceptible} \cap \text{inpatient}) \cdot \sum(\text{infected} \cap \text{inpatient} \cap \text{isolated}')}{\sum(\text{inpatient})}$ |
| Recovery of an infected individual | $\gamma \cdot \sum(\text{infected})$ |
| Detection of an infected in the hospital (i.e. by random screening)* | $\phi \cdot \sum(\text{infected} \cap \text{detected}')$ where $\phi = \frac{\varepsilon \cdot \sigma}{NH}$ |
| Detection of an infected on admission to the hospital (i.e. by on-admission screening)* | $\omega \cdot \sum(\text{ins} \cap \text{infected})$ where $\omega = \frac{\varepsilon \cdot (1-\sigma)}{NA}$ |

***Movement of detected infected individuals occurs automatically following detection when**

$\sum(\text{isolated}) < NISO$

**and** $\sum(\text{infected} \cap \text{inpatient} \cap \text{detected} \cap \text{isolated}') > 0$.

**Table 6.2** Stochastic events and event rates given in terms of sets described in Figure 6.1.

### 6.2.2 Model extension to multi-centre

Exactly the same framework and assumptions were used for the multi-centre model, except the patient population was split into 3 distinct sub-populations representing each of the three hospitals. Again, discharges and admissions were carried out simultaneously on a daily basis and movements around the network simulated the real movements of patients into and out of the three hospitals comprising the UHL NHS Trust from 1998 to 2005 (as described in Chapter 5). Again, infection was added stochastically. Infection could only occur in hospital (not in the community) and, in addition, an infected patient could only infect susceptible patients within the same hospital. The multi-centre model's structure is as that given in Figure 6.1 except the hospital population is split into three

identical hospital populations each with susceptible, infected, detected and isolated sets within it. The stochastic events and their corresponding rates are as those in Tables 6.1 and 6.2, except that the average number of admissions to each hospital per day and average number of patients in each hospital per day are as those given in Table 6.3.

| **Parameter** | **Symbol** | **Value** | **Reference** |
|---|---|---|---|
| Average number admissions/ day to hospital 1 | NA1 | 324 | From dataset (as described in chapters 4 and 5) |
| Average number admissions/ day to hospital 2 | NA2 | 149 | From dataset |
| Average number admissions/ day to hospital 3 | NA3 | 75 | From dataset |
| Average number in hospital 1/ day | NH1 | 781 | From dataset |
| Average number in hospital 2/ day | NH2 | 556 | From dataset |
| Average number in hospital 3/ day | NH3 | 382 | From dataset |
| Overall population size (the population that visits hospital at least once over the study period) | NH1+NH2+NH3+NC | 514159 | From dataset |

**Table 6.3** Parameter values used in the multi-centre model.

The models were written and run in MATLAB® (Version, 7.0, MatLab, The MathWorks, Natick, MA, USA) on a personal computer.

## 6.3 Results

### 6.3.1 Analytical results

#### Single-centre model

To calculate $r_0$ in the single-centre model with realistic patient movement patterns the relationship

$$r_0 = \frac{\beta}{\mu + \gamma},$$

introduced in Chapter 2, can be used. Where β and γ values are as those in Table 6.1, and $1/\mu$ the average length of stay in hospital is calculated from the dataset (given in Chapter 4, section 4.3.2). This calculation is complicated slightly by the fact that in the single-centre simulations admissions and discharges are performed simultaneously; therefore, outpatients effectively leave the hospital instantaneously upon admission meaning they will not contribute to infection within the hospital. Therefore, in calculating $r_0$ and $R_0$, $1/\mu$ is taken as the average length of stay excluding outpatients (6.65 nights). In this way $r_0$ for the single-centre model is calculated to be 1.062, and from this $R_0$ as 1.9 (using

$$R_0 = r_0 \frac{1}{1 - P},$$

where (1/(1-P)) is taken to be 1.79 as calculated from the dataset in Chapter 5).

Using this rationale, whilst β remains the same as the value in Chapter 2, $r_0$ and $R_0$ are different (due to the difference in 1/(1-P) and μ values when calculated from the dataset). For this reason, simulation results were also obtained using altered β values, such that settings in which both $r_0$ and $R_0$ reflect those in Chapter 2 could be explored (all β values and their corresponding $r_0$ and $R_0$ values are given in Table 6.4).

| β | $r_0$ | $R_0$ |
|---|---|---|
| 0.1126 | 0.74 | 1.32 (as in chapter 2) |
| 0.1622 (as in chapter 2) | 1.06 | 1.90 |
| 0.1939 | 1.27 (as in chapter2) | 2.27 |

**Table 6.4** Range of β values used in 'real-movements' model simulations and their corresponding $r_0$ and $R_0$ values.

**Multi-centre model**

To calculate the within-hospital reproduction number ($r_0$) for each individual hospital in the multi-centre model, the relationship

$$r_{0_i} = \frac{\beta_i}{\mu_i + \gamma_i}$$

can be used (where i refers to the hospital number). Using the parameter values as described in Table 6.5, $r_0$ for hospitals 1, 2 and 3 can be calculated to be 0.92, 1.14 and 1.36 respectively.

| Parameter | Symbol | Value | Reference |
|---|---|---|---|
| Transmission coefficient hospital 1 | $\beta_1$ | 0.1622 | As in chapter 2 |
| Transmission coefficient hospital 2 | $\beta_2$ | 0.1622 | As in chapter 2 |
| Transmission coefficient hospital 3 | $\beta_3$ | 0.1622 | As in chapter 2 |
| Discharge rate ($day^{-1}$) hospital 1 | $\mu_1$* | 0.174 | From dataset (section 4.3.2) |
| Discharge rate ($day^{-1}$) hospital 2 | $\mu_2$* | 0.140 | From dataset (section 4.3.2) |
| Discharge rate ($day^{-1}$) hospital 3 | $\mu_3$* | 0.117 | From dataset (section 4.3.2) |
| Recovery rate ($day^{-1}$) hospital 1 | $\gamma_1$ | 0.0027 | As in chapter 2 |
| Recovery rate ($day^{-1}$) hospital 2 | $\gamma_2$ | 0.0027 | As in chapter 2 |
| Recovery rate ($day^{-1}$) hospital 3 | $\gamma_3$ | 0.0027 | As in chapter 2 |

**Table 6.5** Values for β, μ, γ used to calculate individual hospital $r_0$ values in the multi-centre model. *$1/\mu_i$ = LOS in hospital i, where i = 1, 2, 3.

The calculation of the overall $R_0$ for the multi-centre model uses a matrix of P values of the form

$$\begin{bmatrix} P_{11} & P_{12} & P_{13} \\ P_{21} & P_{22} & P_{23} \\ P_{31} & P_{32} & P_{33} \end{bmatrix} = \begin{bmatrix} 0.66 & 0.10 & 0.15 \\ 0.04 & 0.52 & 0.07 \\ 0.03 & 0.04 & 0.40 \end{bmatrix}$$

where, for example, $P_{12}$ is the probability of an infected individual being discharged from hospital 1 and readmitted to hospital 2 while still infected. These probabilities are calculated using the distribution of all readmissions (n= 887312) and numbers of infectious readmissions (calculated as described in section 5.3.4 using a negative exponential distribution of recovery with a mean recovery rate of 0.0027/day).

From this $Q_{ij}$ is calculated, where $Q_{ij}$ is the probability of an infectious admission to hospital j (at some point) given an infectious discharge from hospital i, where i,j = 1,2,3. $Q_{ij}$ differs from $P_{ij}$ in that $Q_{ij}$ incorporates all infectious admissions to hospital j by an infectious individual initially infected in hospital i *via any route* (i.e. rather than just directly) over the entire period they are colonized. For example, considering the schematic in Figure 6.2, if an infected individual were to be discharged from hospital 2, then the total number of infectious cases they would cause in hospital 1 would be the sum of the infectious cases caused by the three hospital episodes in hospital 1 (from admissions A, B and C), providing they remain colonized throughout this period.

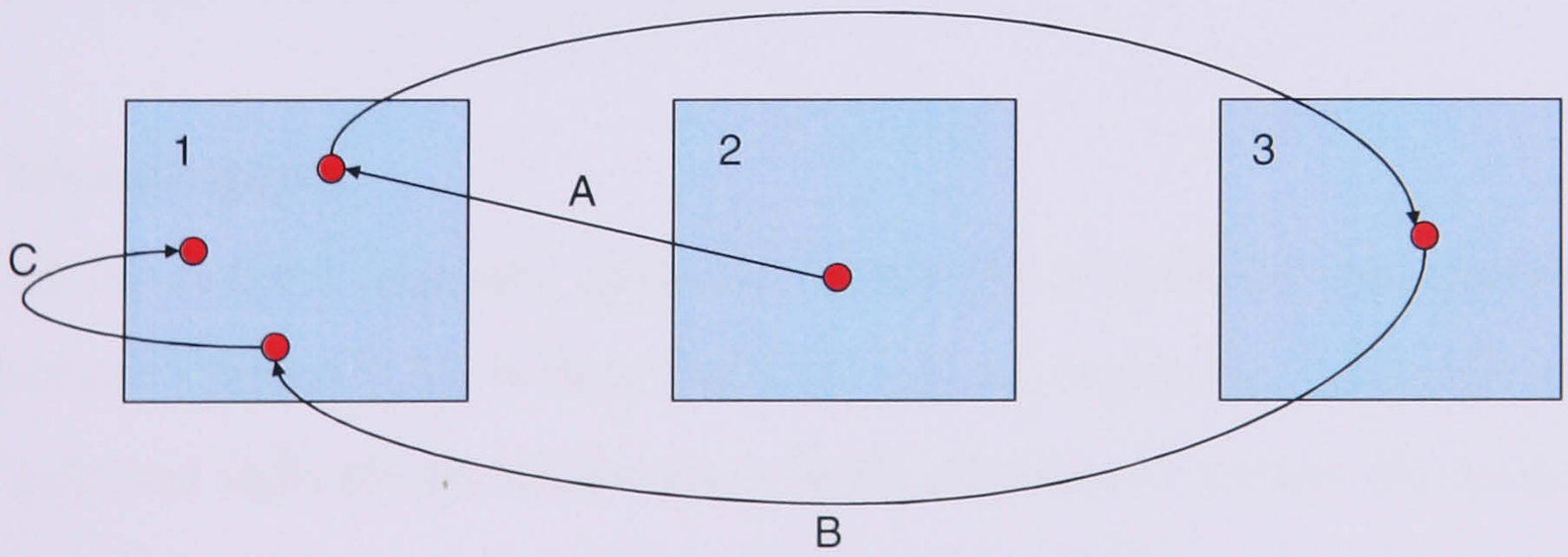



**Figure 6.2** Schematic diagram of the readmission history of one infected individual within and between three hospitals (1, 2 and 3). Where A = $P_{21}$, B = $P_{31}$ and C = $P_{11}$.

Clearly, to calculate the total number of secondary infections in hospital 1 caused by an individual initially infected in hospital 2 considering only $P_{21}$ would be insufficient as the total number of infectious cases caused in 1 is also dependent on $P_{31}$ and $P_{11}$. Instead $Q_{21}$ is used, in which each possible route of entry to hospital 1 from hospital 2 is considered. The matrix for Q is given by

$$\begin{bmatrix} Q_{11} & Q_{12} & Q_{13} \\ Q_{21} & Q_{22} & Q_{23} \\ Q_{31} & Q_{32} & Q_{33} \end{bmatrix} = \begin{bmatrix} 0.67 & 0.04 & 0.03 \\ 0.11 & 0.53 & 0.04 \\ 0.16 & 0.07 & 0.40 \end{bmatrix}.$$

Equations for $Q_{ij}$ are given in Appendix 2. From this an $R_{ij}$ matrix can be established, where $R_{ij}$ is the average number of secondary infections in hospital j caused by an infected individual initially infected in hospital i, using

$$R_{ij} = r_{0_i}\left(\frac{1}{1-Q_{ij}}\right)$$

where i = j, and

$$R_{ij} = Q_{ij}R_{jj}$$

otherwise (full equations given in Appendix 2).

Giving

$$\begin{bmatrix} R_{11} & R_{12} & R_{13} \\ R_{21} & R_{22} & R_{23} \\ R_{31} & R_{32} & R_{33} \end{bmatrix} = \begin{bmatrix} 2.75 & 0.11 & 0.08 \\ 0.30 & 2.43 & 0.09 \\ 0.44 & 0.18 & 2.28 \end{bmatrix},$$

in turn giving an overall $R_0$ for the multi-centre network of 2.9.

### 6.3.2 Single-centre model results

#### Without control

With no control imposed upon the infectious population an epidemic pattern is observed (Figure 6.3). Within the first year an exponential increase in the number of infected individuals within the overall population occurs. Endemic equilibrium is reached within 4 years, where approximately 25000 individuals (of a population of size 514159) are infected. Infected individuals in the hospital reach equilibrium (~750 infected patients) within the first 2 to 3 years.

In terms of surveillance, although both strategies (random and on-admission) are able to detect infected patients, random screening is by far the most efficient strategy. At a 70% effort level random screening is able to detect approximately 70% of infected patients. Whereas on-admission screening detects approximately a quarter of the infected patient population, even once endemic equilibrium is reached in the community.

On varying the transmission parameter $\beta$ according to the values calculated in Table 6.4, in order to give $r_0$ and $R_0$ values that reflect those in the stochastic model (in Chapter 2), endemic behaviour is seen to occur with each $\beta$ value (Figure 6.4). Reducing $\beta$ (and therefore $r_0$ and $R_0$) has the effect of increasing the time taken to reach endemicity and decreasing the value at which endemic equilibrium is achieved. As may be expected, increasing $\beta$ (and therefore $r_0$ and $R_0$) has the opposite effect i.e. decreasing the time taken to reach endemicity and increasing the value at which endemic equilibrium is achieved. These patterns are observed in both the hospital and community populations.

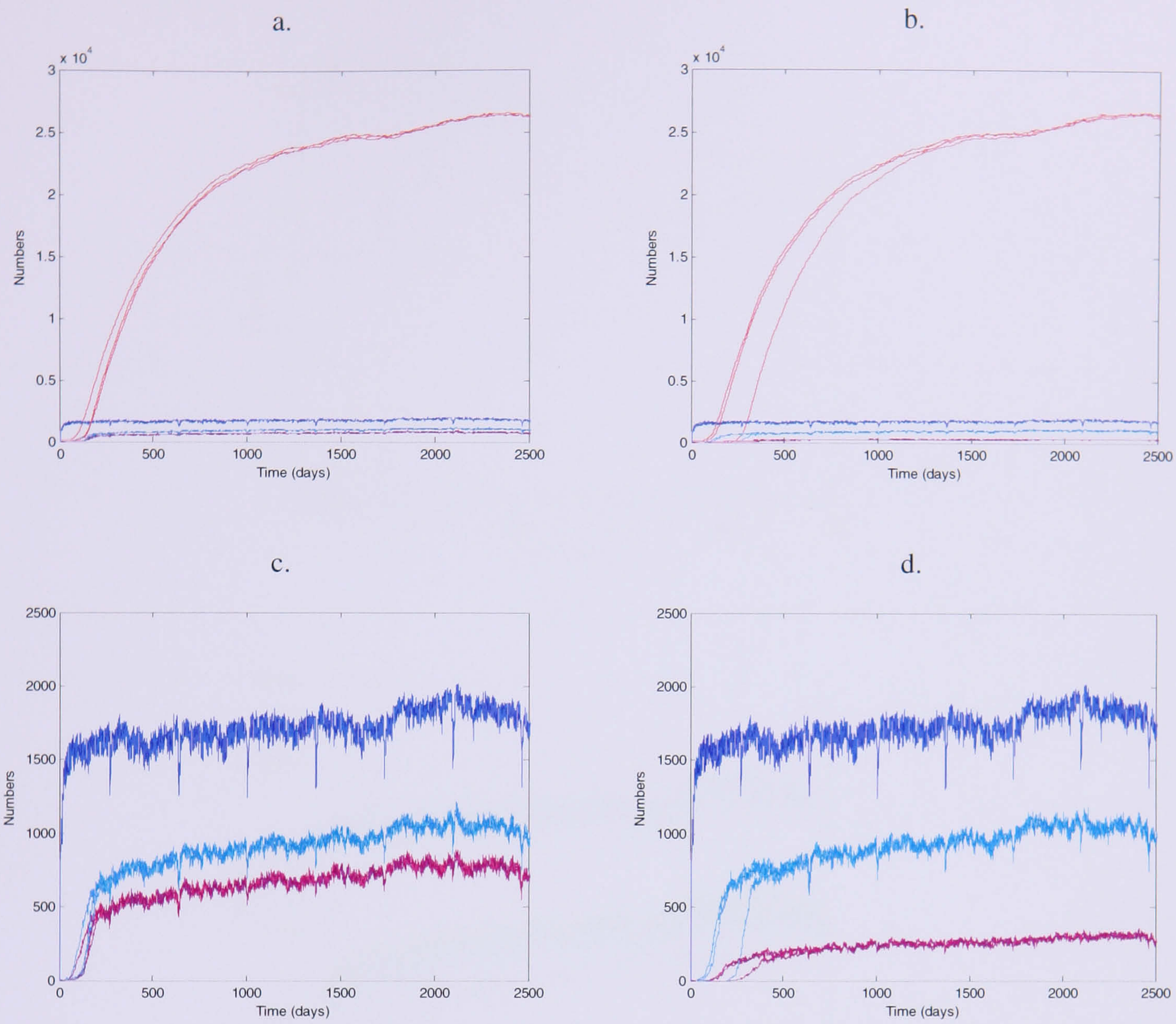
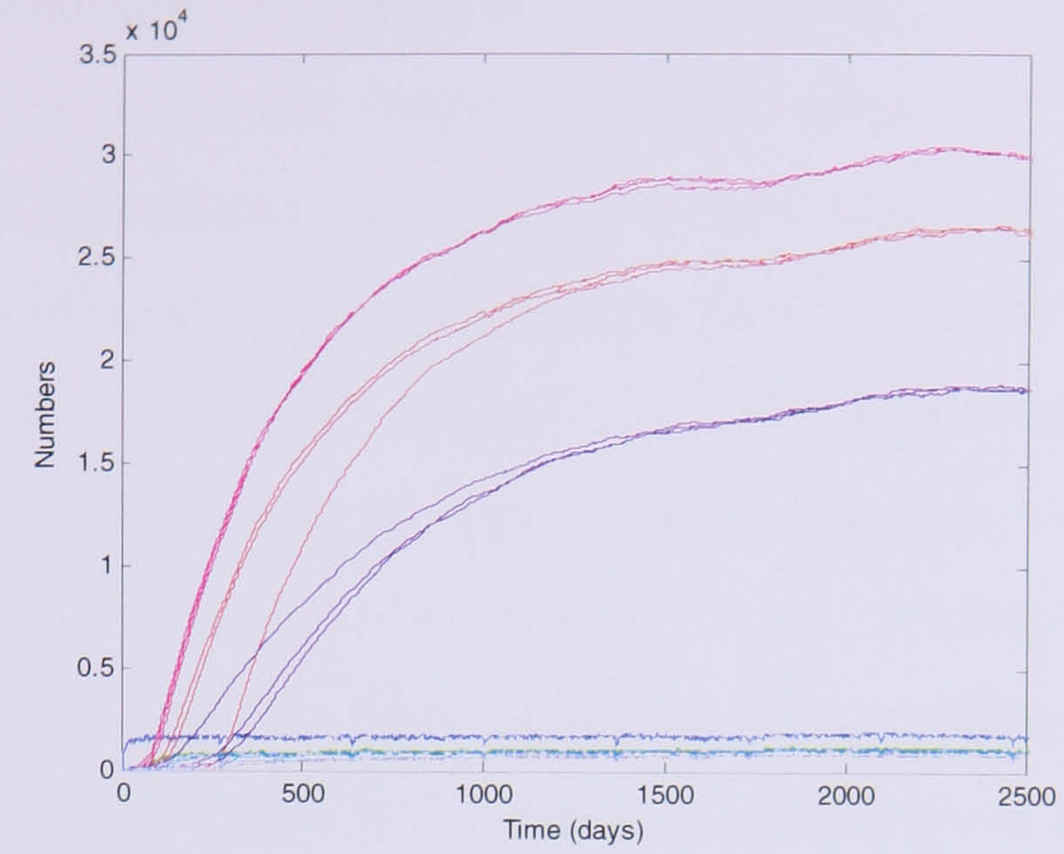



**Figure 6.3** Simulation results over ~7 years (2500 days) with no control strategy imposed. All parameter values are as those given in Table 6.1. Panels each show three simulations where, a) and b) depict infection and detection within both the hospital and community populations and panels c) and d) show the same data for the hospital population only. For panels a) and c) the surveillance strategy is 100% random screening, whereas for panels b) and d) surveillance is 100% on-admission screening (both screening strategies were set at a 70% effort). Where: — = inpatient; — = infected; — = inpatient & infected; and — = inpatient & detected.

a.




b.

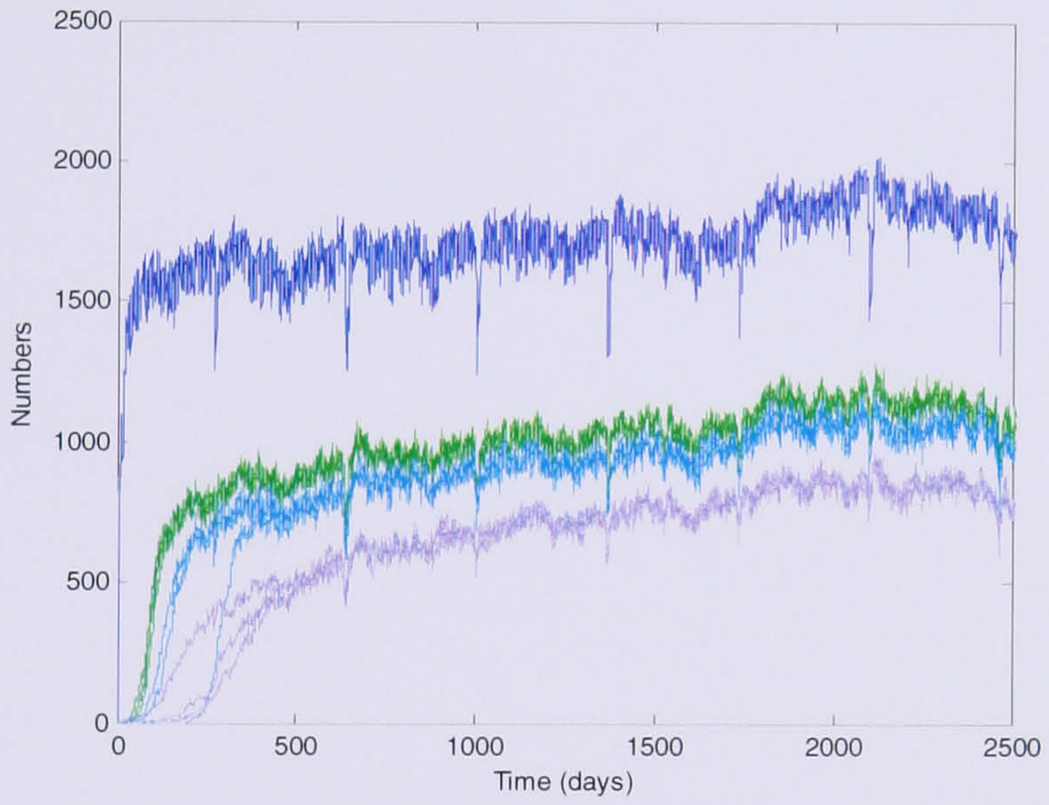
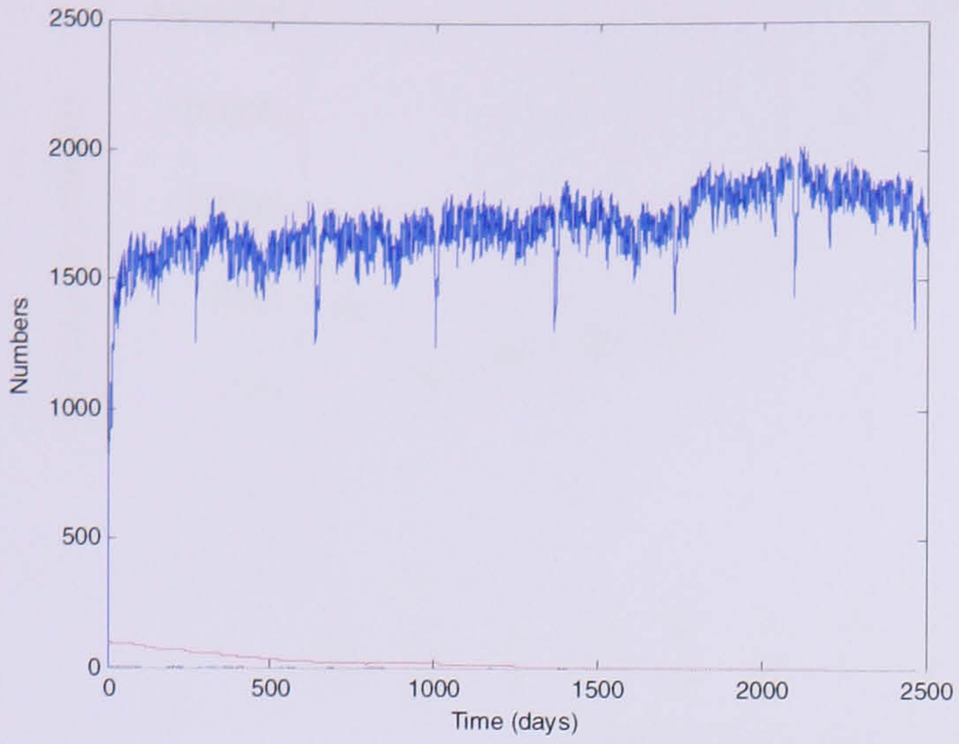



**Figure 6.4** Simulation results over ~7 years (2500 days) in which the transmission parameter (β) is varied and no control is imposed. β is varied according to the values given in Table 6.4 and all other parameters are as those given in Table 6.1. Panels each show three simulations of each transmission parameter where, a) depicts infection and detection within both the hospital and community populations and b) the same data for the hospital population only.
Where: — = inpatient; — = infected when β=0.1939; — = infected when β=0.1622; — = infected when β=0.1126; — = inpatient & infected when β=0.1939; — = inpatient & infected when β=0.1622; and — = inpatient & infected when β=0.1126.

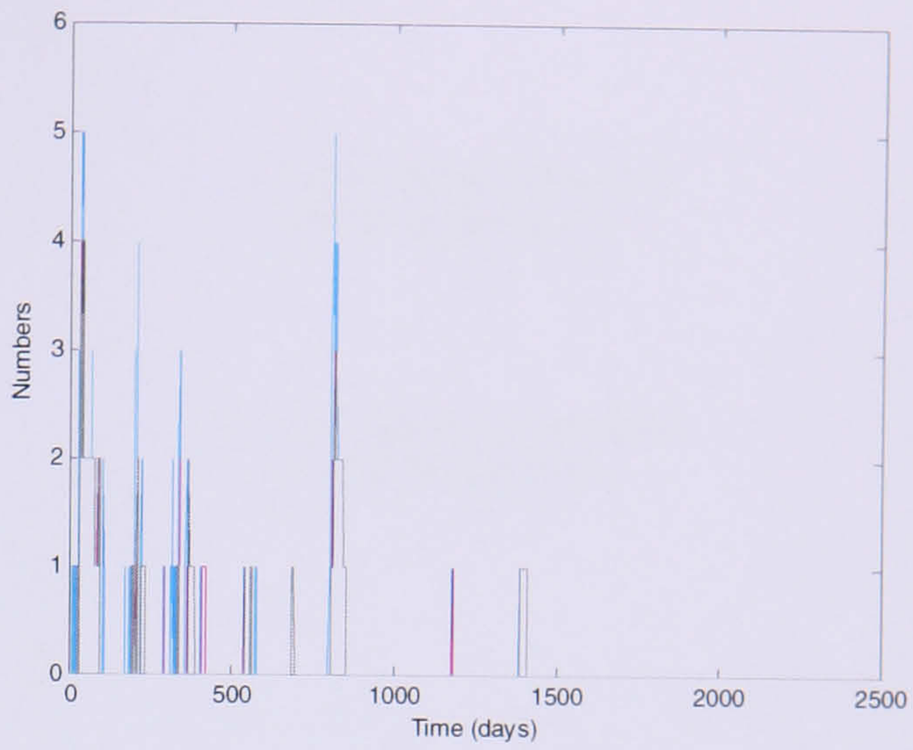
**Control of epidemic**

Control is clearly exhibited by random screening and a 50/50 combination of random and on-admission screening, whereas a strategy solely comprised of on-admission screening does not control infection (Figure 6.5). Looking at the interplay between surveillance and control in more detail (Figure 6.6), generally the greater degree of random screening employed, the greater the level of control achieved. However, rather than a strategy of 100% random screening to 0% on-admission screening, a strategy of 90% random screening to 10% on-admission screening seems to be optimal. An increase in the proportion of on-admission screening that makes up the 70% screening effort results in more infected individuals within the hospital and a reduced capability of detecting them (the sum of the detected patients in hospital begins to deviate from the sum of the infected patients in hospital).

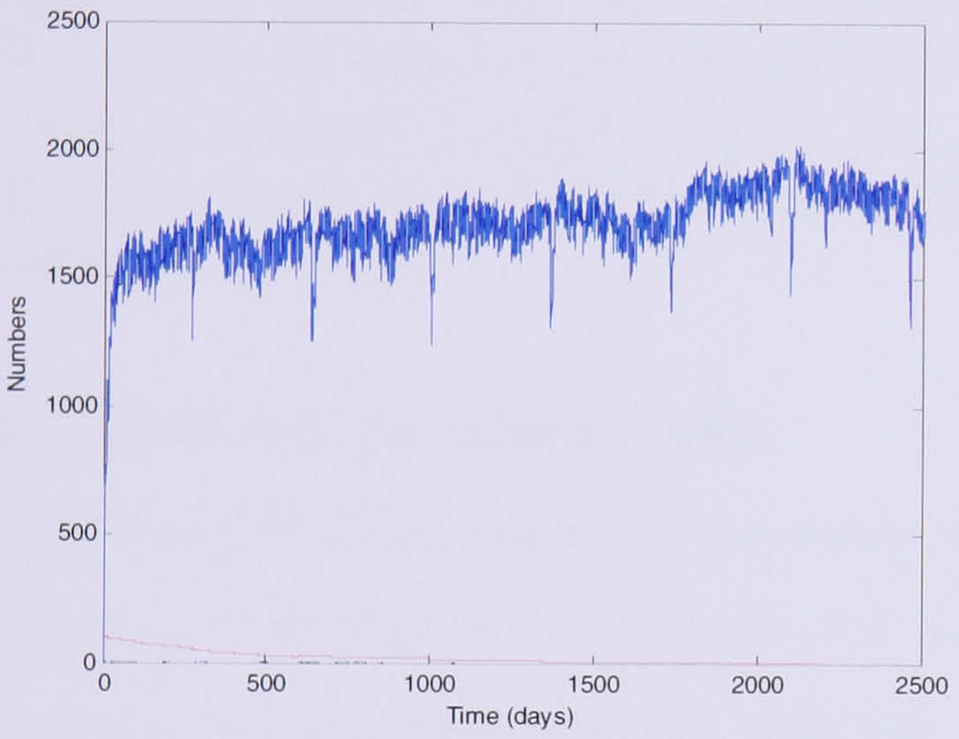
a.



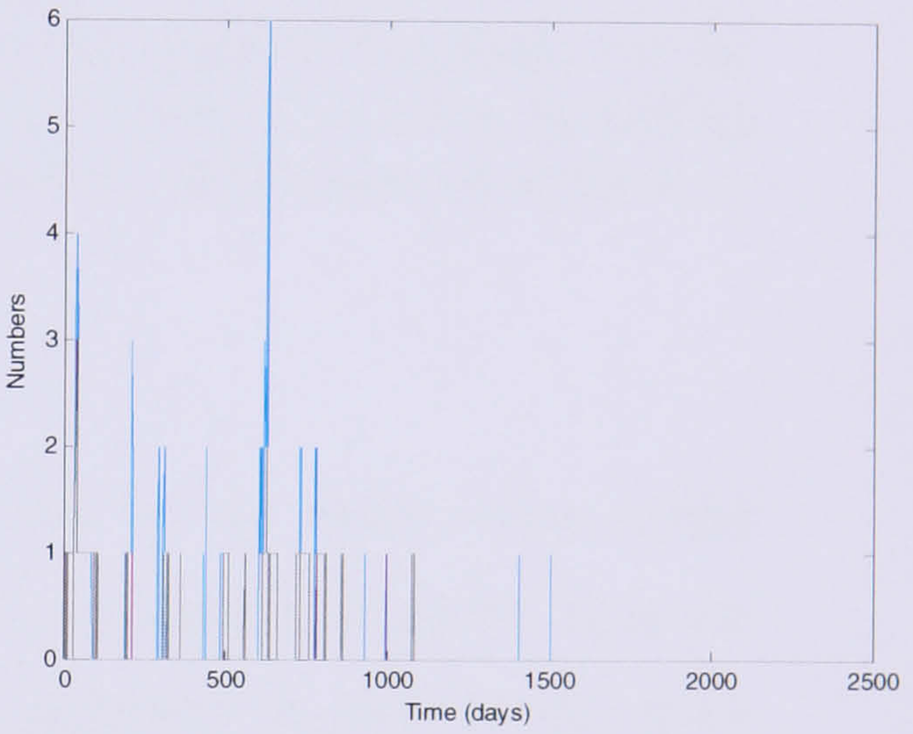

b.



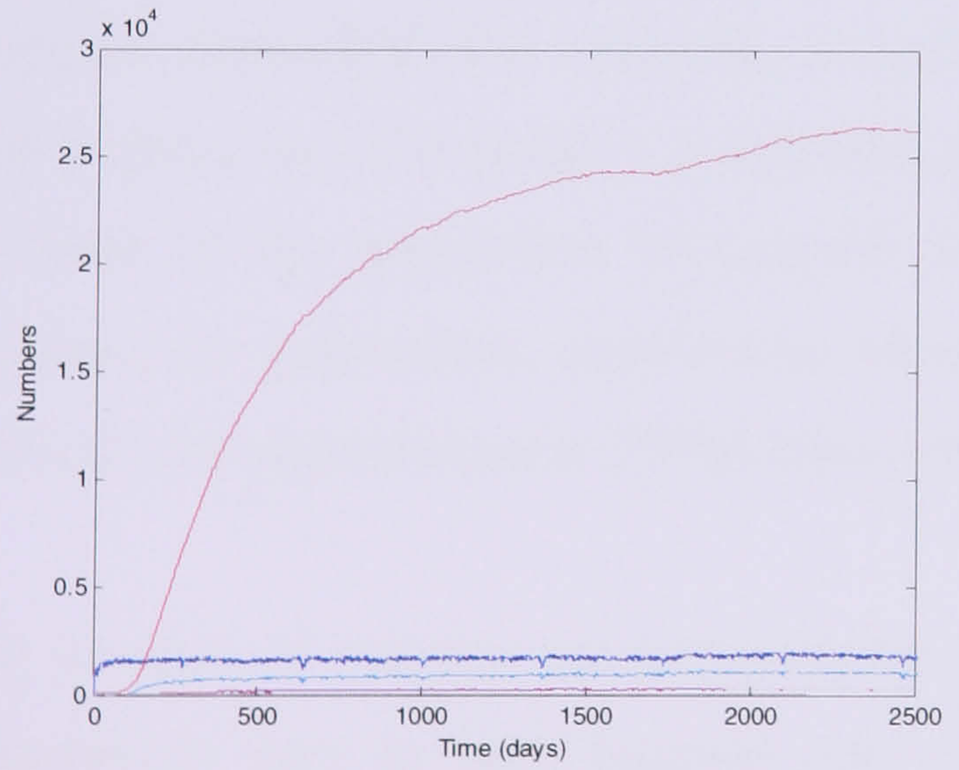

c.




d.




e.




f.

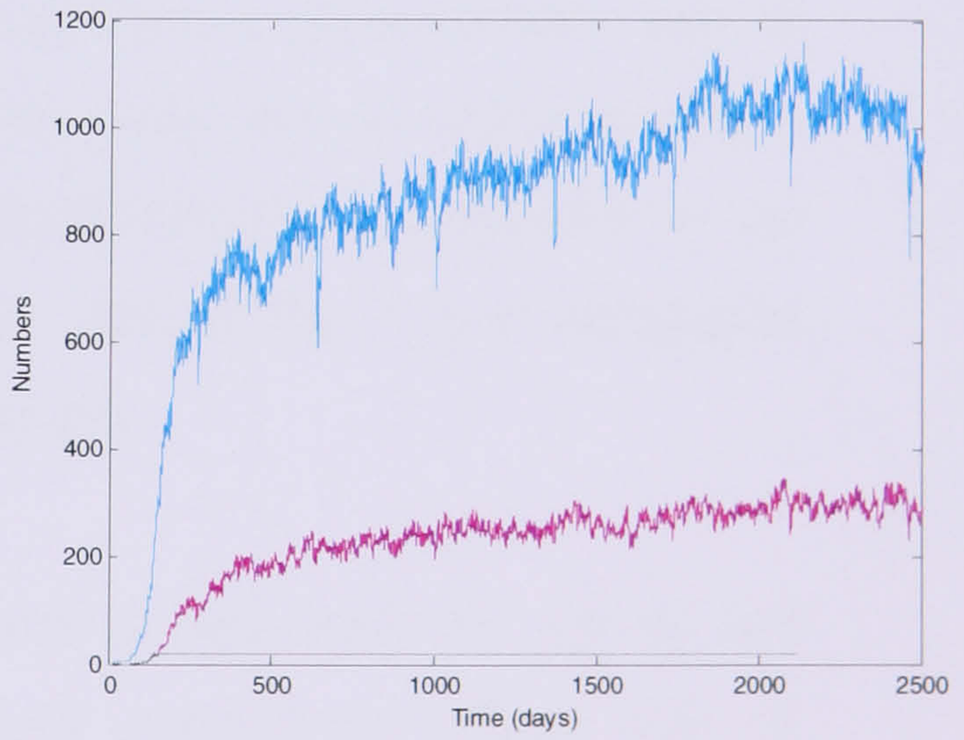



**Figure 6.5** Simulation results over ~7 years (2500 days) comparing combinations of random and on-admission screening alongside an IW (capacity 20). Parameters are as those given in Table in 6.1. Panels a) and b) depict 100% random screening, c) and d) 50% random/50% on-admission screening, e) and f) 100% on-admission screening. Where: — = inpatient; — = infected; — = inpatient & infected; — = inpatient & detected; and — = isolated.

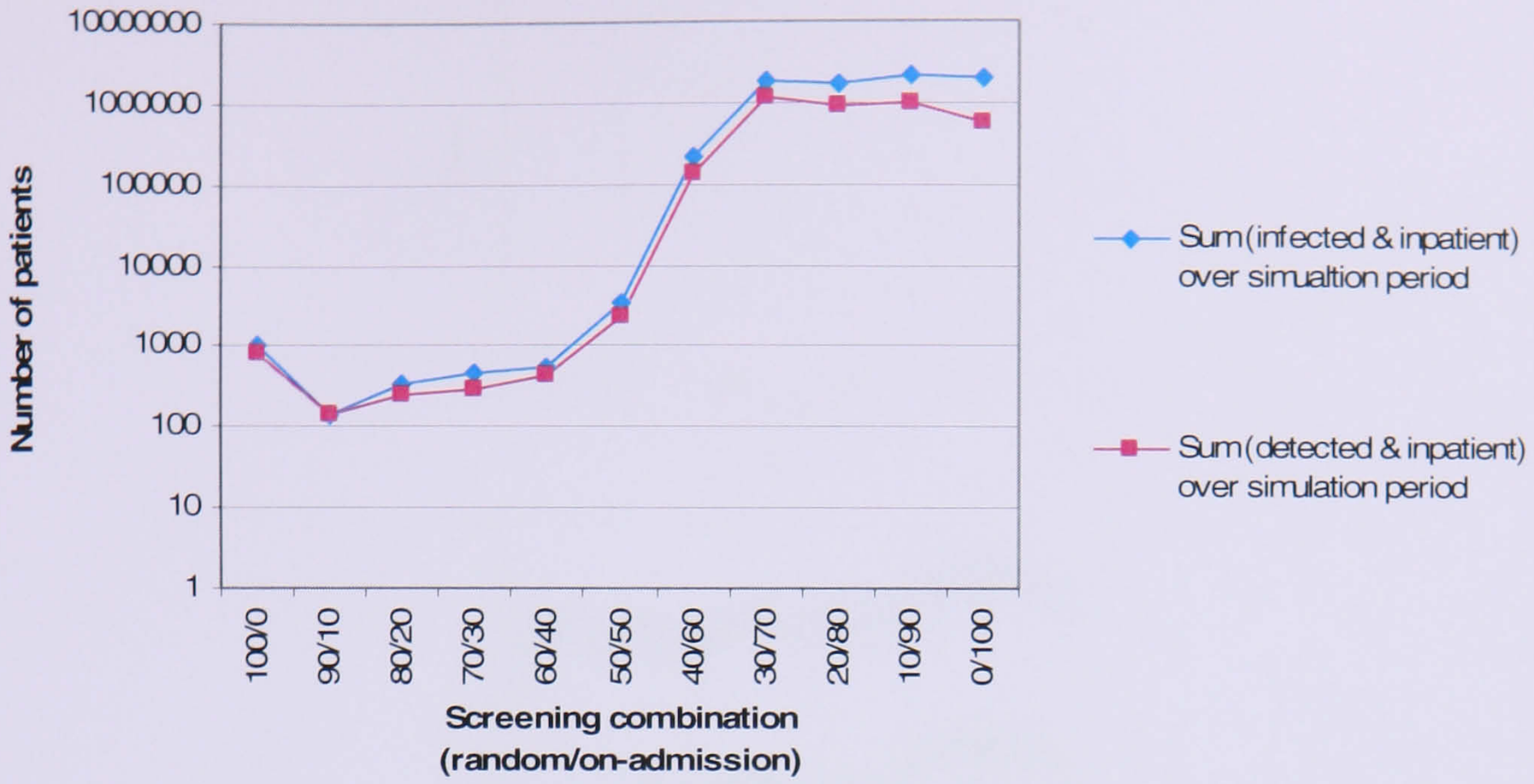


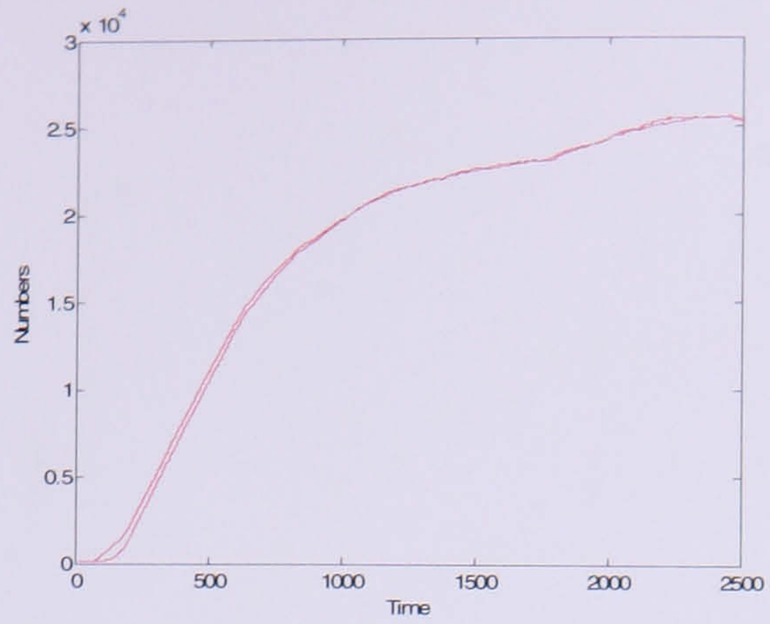

**Figure 6.6** Relationship between screening strategy and detection and control. The number of infected and detected individuals in the hospital summed over the 7 year simulation period is plotted, averaged over 5 simulation runs. Screening effort was made up to 70% in every combination and all parameters set to those in Table 6.1.

### 6.3.3 Multi-centre model results

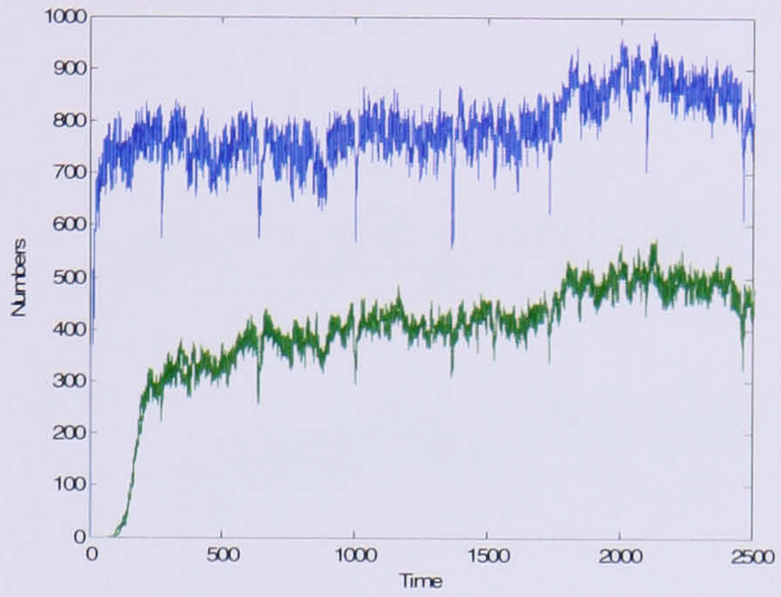
With no control imposed the epidemic patterns seen for the multi-centre model (Figure 6.7) appear similar to those for the single-centre model (Figure 6.3) in the community population and an endemic state is achieved in each of the three hospitals (Figure 6.7). However, the individual hospital prevalence is seemingly hospital dependent. For example, at endemic equilibrium approximately half of the population of hospital 1 is colonized/infected compared to approximately a seventh of the population of hospital 2. Epidemic behaviour exhibited in the community approaches equilibrium towards the end of the 7 year simulation period with approximately 25000 infected individuals.

As a result of varying the transmission parameter $\beta$ both epidemic timing and magnitude vary in both hospital and community populations (Figure 6.8). A decrease in transmission rate results in a slower epidemic with a lower prevalence throughout the simulation period. This effect is seen most markedly in the community population but also occurs in each individual hospital within the network.

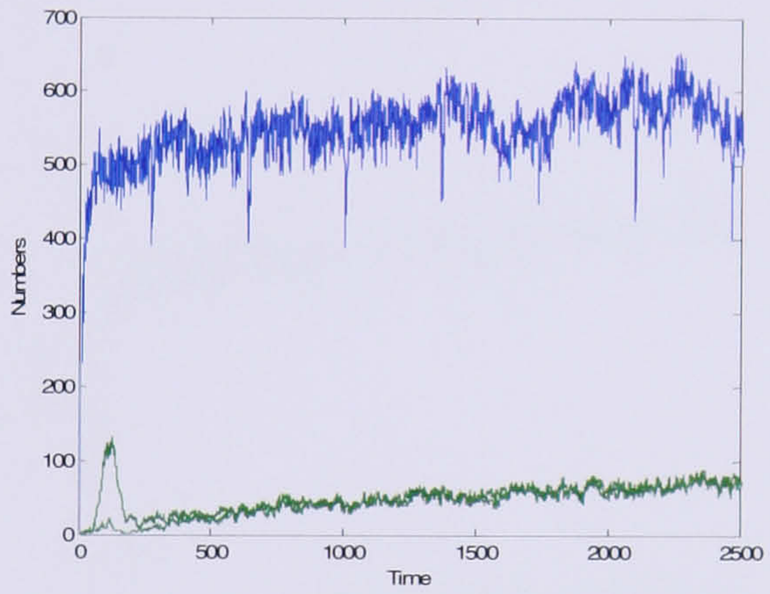
a.




b.




c.




d.

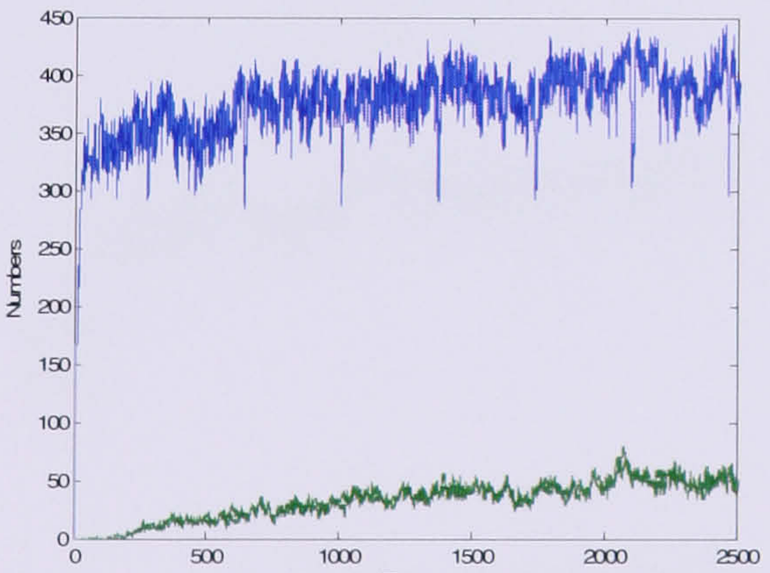
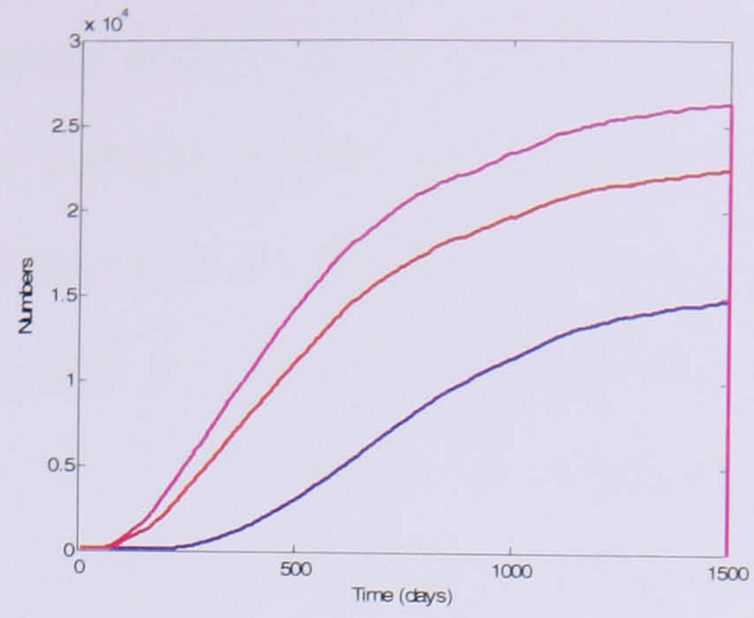
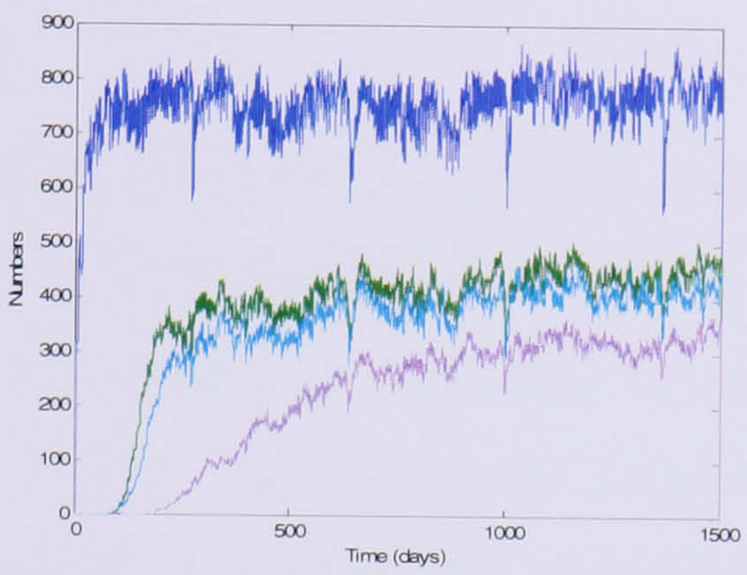



**Figure 6.7** Five multi-centre simulation results (over ~7 years) with no control strategy imposed. Parameter values are set to those in Table 6.1 except average admissions and population sizes which are as those in Table 6.3. Panel a) depicts the community population, b) hospital 1, c) hospital 2 and d) hospital 3. Where: — = inpatient; — = infected and — = inpatient & infected.

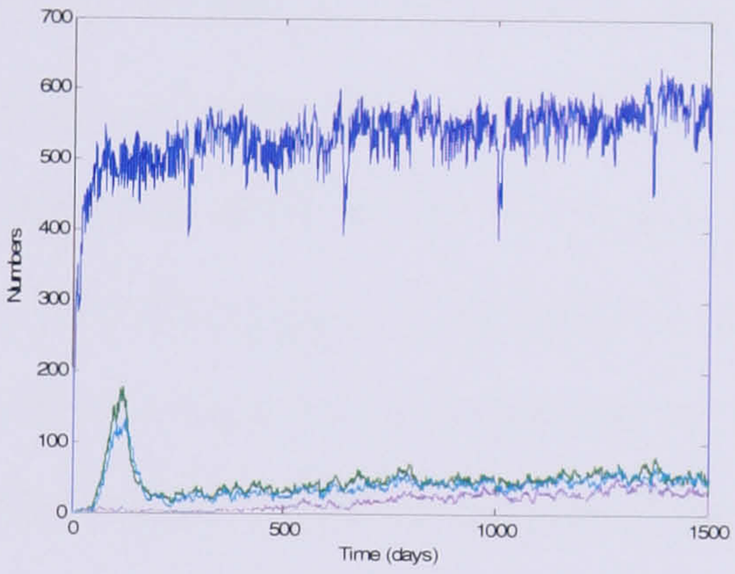
a.




b.




c.




d.

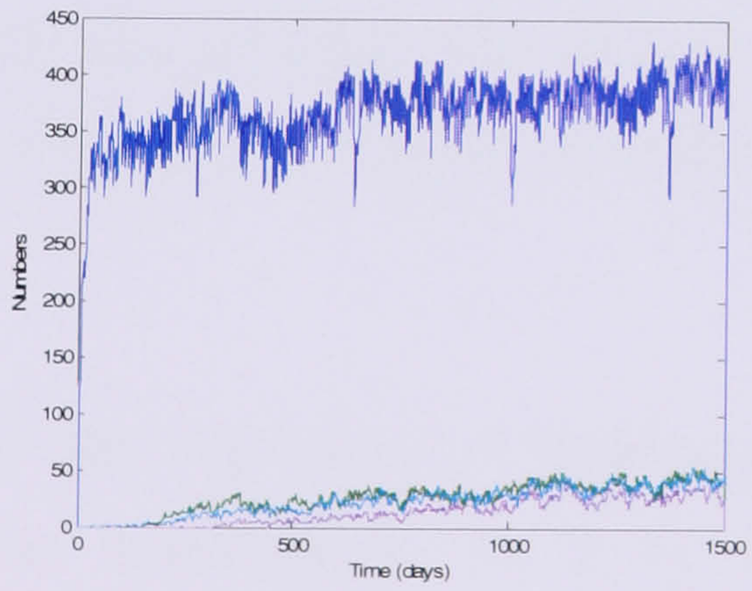



**Figure 6.8** Five simulation results (over ~4 years) in which the transmission parameter (β) is varied between runs and no control is imposed. Parameter values are as those in Tables 6.1 and 6.3. Panel a) depicts overall infection prevalence (including that in the community), b) hospital 1, c) hospital 2 and d) hospital 3. Where: — = infected (β = 0.1939); — = infected (β = 0.1622); — = infected (β = 0.1126); — = inpatients; — = inpatient & infected (β =0 .1939); — = inpatient & infected (β = 0.1622); — = inpatient & infected (β = 0.1126).

## 6.4 Discussion

The purpose of this chapter was to develop a model to investigate transmission dynamics and infection control of HCAI given a setting of real movements between hospital and catchment populations. In this way the findings in Chapter 5 regarding the increase in probability of infectious readmissions (compared to that used in previous models) will be inherent. In addition, heterogeneities in patient readmission rates, with some demographic groups more likely to return to hospital, will also be integrated.

The results from the single-centre real-movements model, in which the Trust is modelled as a whole and transmission between all inpatients possible, show little variability. Endemic equilibrium is consistently reached in both hospital and community populations within the seven year simulation period (Figure 6.3). However, as stated in Chapter 5, in using the real admission/discharge dataset to determine patient movements in and out of hospital this model creates a setting in which infected readmissions are more likely. In effect, the value of the parameter P has increased compared to that used in the stochastic model described in earlier chapters. This change in P has the effect of altering $r_0$ and $R_0$ for these simulations (given that all other parameter values are assumed to remain the same as those used in the stochastic model). The effect of changing the value of the transmission parameter ($\beta$) in order to create settings in which $r_0$ and $R_0$ reflect those in previous stochastic models was to change both the time until endemic equilibrium was reached and also to change the prevalence attained at this equilibrium (Figure 6.4).

These results emphasise the importance of heterogeneity in admissions. By extension, there will be heterogeneity in $\beta$ by individual (in terms of infectiousness and susceptibility), length of stay, hospital and specialty for example. This uncertainty over the transmission parameter requires some further consideration, for example by sensitivity analysis to determine the extent to which dynamic behaviour is dependent on it. Furthermore, although not attempted here, analysis of infection data would enable estimation of heterogeneities in

transmission and the impact of these heterogeneities on transmission dynamics. In addition, the effect of the initial conditions on these dynamics needs to be considered, especially as the only variability seen in the single-centre model results occurs in the initial stages of the simulations.

It was predicted that in a more realistic setting, i.e. with an increase in patient movements, on-admission screening may be the preferred infection control strategy. The probability of infectious readmissions for the single-centre model (calculated from the hospital dataset) was 0.44, giving, on average, 1.8 infectious readmissions per infected patient. For this parameter value the analytical results in Figure 2.3 (Chapter 2) show a strategy comprised of 50% random screening/50% on-admission screening to give control provided the equivalent of at least 70% of hospital admissions are screened, a strategy comprised of 100% on-admission screening giving control only when all patients are screened and 100% random screening giving control with a screening effort of 80% or greater. The simulation results for the single-centre model, under these screening strategy combinations, seem to reflect these analytical predictions (Figure 6.5). Strategies comprised of 100% random screening and 50%/50% random/on-admission screening (Figure 6.5 a, b, c, d) exhibit control. Whereas epidemic behaviour is seen when screening is solely on-admission (Figure 6.5 e and f).

It is worth noting that the $r_0$ value in these simulations is greater than 1, whereas the analytical results in Chapter 2, Figure 2.3 (to which the simulation results are compared) apply to an $r_0$ value of 0.98. However, as a 70% screening effort applied to an entirely on-admission based screening strategy was inadequate at controlling infection when admissions were necessary for infection to persist (the analytical results) it seems unlikely that control would occur when infection could persist irrespective of infectious admissions (simulation results).

Again, similarly to the results seen in Chapter 3, the capability of control can be explained by the surveillance capability. Random screening within the hospital is more effective at surveillance than screening on-admission which detects few of

the infected individuals (even when infectious admissions from the community epidemic are at their highest) (Figure 6.3 panel c compared to panel d) and this surveillance capability translates to hospital and community control (Figure 6.5). When the total number of detected individuals is compared to the total number of infected individuals (Figure 6.6) it can be seen that a greater proportion of random screening (in any random/on-admission screening strategy) has two outcomes: firstly, it gives a greater degree of control and secondly, the number of detected individuals more closely reflects the number of infected individuals. Again, as in the results seen in Chapter 3, on-admission screening as well as being less able to control infection, is also less able to detect this control failure. Despite on-admission screening being less effective than may have been predicted in the analytical results for settings of such high patient movements, a control strategy of 100% random screening is less effective at control than a strategy incorporating a small degree of on-admission screening, with a strategy focusing 10% of its effort on reducing infectious admissions and 90% on reducing within-hospital transmission found to be optimal (Figure 6.6).

When the Trust is modelled as three distinct hospital populations, with patient movements around the healthcare network occurring according to the admission/discharge data, variability in epidemic pattern between hospitals can be seen (Figure 6.7).

All hospitals exhibit endemicity, however proportionally hospital 1 has a greater prevalence than that in hospitals 2 and 3. Despite hospital 1 having the lowest within-hospital $r_0$, this behaviour can be explained through the greater numbers of admissions and readmissions to hospital 1 (Figures 4.5 and 5.5). This suggests potential importance of patient movement patterns in the transmission dynamics of HCAI; certain hospitals may be at a higher risk of MRSA infection simply due to the patient movement patterns.

The fact that the sum of the prevalences at each individual hospital in the multi-centre model is not equal to the overall hospital prevalence for the single-centre

model is to be expected due to the inclusion of between hospital heterogeneities. Generally, however, it seems that the patient population benefits from there being three individual hospitals as opposed to one pooled population (i.e. the proportion of infected individuals at the hospital with the greatest prevalence (hospital 1, shown in Figure 6.7, panel b) is still less than that for the single-centre model).

The consistency of epidemic pattern between simulations is striking (Figure 6.7). This lack of variability is to be expected as in each simulation the same individuals are initially infected and their subsequent movements around the network are identical across simulations. Any variability that occurs is due only to the stochastic nature of within-hospital transmission events and both hospital and community recovery events (the rates of which also remain constant across simulations).

It is likely that each individual hospital would have a different transmission coefficient value, unlike the assumption in the multi-centre model where a single value is used. However, without good infection data these $\beta$ values cannot be estimated. Investigations into sensitivity to the transmission parameter (Figure 6.8) demonstrate that epidemic patterns are sensitive to variations in the transmission rate. Further work in this area would help to give more precise and hospital specific transmission parameter estimates, which would in turn allow a greater understanding of the comparative effects of hospital driven and admission/readmission driven dynamics and how these effects may influence control strategy success.

The degree to which the hospital epidemics shown are fuelled by readmissions from their own population compared to transfers from other hospitals could also be investigated further. The majority of patients returned to their hospital of discharge (as described in Chapter 5 (Table 5.2)) and so constrained transmission to one particular hospital. However, it seems that an approximately 20% chance of between hospital transfer on readmission (as was found to be the case for UHL NHS Trust) is sufficient to maintain infection throughout the network. These

results suggest that neighbouring hospitals with a shared catchment population help to maintain persistence throughout the network. This agrees with previous work in which endemic behaviour is achieved and sustained with transfer of infection between hospitals and the community (Smith *et al.*, 2004; Austin and Anderson, 1999a) and, in turn, the resulting community reservoir further helping in persistence of hospital outbreaks (Cooper *et al.*, 2004a).

An interesting extension of this model would be to vary the transmission rate in individual hospitals in order to investigate the extent to which contributions to the infectious community reservoir from surrounding hospitals influence the epidemic pattern seen at a particular hospital. Clearly, in terms of control, it is important to determine whether epidemic behaviour in one hospital is partially dependent on its neighbours and therefore whether the success of control within each individual hospital could have a more far-reaching impact than just its own population.

Further work needs to be undertaken to explore the dynamics within a multi-centre setting, especially in the context of infection control. For the model presented here, the effects of initial conditions and parameter values need to be considered. In addition, including patient heterogeneity within the model would allow effects such as difference in susceptibility by age, gender and specialty to be explored.

# Chapter 7

# Discussion and Conclusions

HCAI pose a major threat to public health yet strategies for their control remain varied between hospitals and healthcare institutions. With a lack of well performed intervention trials it is unclear which strategies would be best to adopt. This research addresses the potential of mathematical modelling for furthering our understanding of HCAI transmission and as a tool for infection control strategy assessment.

Furthermore, analyses of real hospital data, carried out to inform model development, help to provide an understanding of the setting in which transmission and control occur. Despite the fact that the dynamics and behaviour of pathogens (particularly drug-resistant strains) are governed by a complex network of, potentially poorly understood, interactions in settings where chance events and variability is likely, research that allows any of these factors of influence to be identified or more clearly understood increases our ability to combat the problem.

**Use of a stochastic model to further understand transmission and control of healthcare associated infections**

Chapters 2 and 3 showed that the development of a mathematical model, incorporating knowledge of the biology, natural history, epidemiology, transmission and control of an infectious organism, can be used to further our understanding of HCAI. The model presented explores transmission of an

antibiotic-resistant pathogen, and in terms of the assumptions and parameter estimations used, the model applies particularly to MRSA. For example, transmission relies on contact between individuals and the reservoir of infection is made up of both infected and colonized individuals. The novel aspect of this research is that the model includes both hospital and community populations as well as movement between them. By including the exploration of both surveillance and infection control within a single framework, this research examines transmission and control in a heterogeneous population. Due to this consideration of both hospital and community populations the overall reproduction number ($R_0$) included two components: one to capture within-hospital transmission ($r_0$) and the other to capture the effects of transmission caused by movement between the hospital and community populations ($1/(1-P)$). The simulations presented show infection progression over long time scales (5 years) and therefore incorporate the previous hospitalisation history of patients - an important factor in both acquisition and transmission of MRSA.

Control strategy assessment provided results that, on initial inspection, seemed counter-intuitive: randomly screening within the hospital population served to reduce spread of HCAI more effectively than screening patients on hospital admission. This result was looked at in detail from the perspective of both surveillance and control and the interplay between them. It was found that given the same control capability, the effectiveness of surveillance was integral to the effectiveness of control; essentially, effective surveillance translated to effective control. Random screening most accurately estimated true prevalence, this detection capability permitting successful within-hospital control, in turn allowing control within the community population. In this case fixed control capacity was brought about by the presence of an IW, but this can be generalised and essentially represents the ability of a hospital (i.e. the resources available) to reduce transmission. Therefore, as well as effective control measures, such as isolation or increased handwashing compliance for example, surveillance was found to be an important component of infection control implying that it should be considered during strategy design.

In addition to allowing control, effective surveillance also allows quantification of control success. Conversely, inadequate surveillance will not only prevent control, but will be unable to detect control failure, and therefore the resulting epidemic may go unnoticed; ineffective surveillance can only ever detect a small proportion of the total number of infected individuals and can therefore easily give the impression that only a few individuals are actually infected. This outcome has the potential to influence HCAI epidemic behaviour and any surveillance strategy should aim to achieve estimates of the number of infected individuals that reflect true hospital infection levels. If an increase in the effort put into detection increases the number of infected individuals detected, then the surveillance effort is not adequate.

The seemingly counter intuitive result of random screening being of more benefit than on-admission screening was explained in terms of the degree of movement by patients between the hospital and community populations. Analytical results showed the optimal screening strategy to be highly dependent on the degree of mixing between populations, quantified in terms the readmission rate of infectious patients. In a setting of low readmission rates the infectious assault posed by the community population is correspondingly low and so concentrating on control within the hospital population (i.e. within-hospital screening) was the most beneficial strategy. In contrast, prevention of infectious admissions from the hospital by on-admission screening should be a greater priority when readmission rates are higher. The simulation results in Chapter 3 use specific parameter values which create a setting of low patient readmission, therefore it is to be expected that on-admission screening has little effect on HCAI infection control.

When considered in terms of the overall reproduction number the effect of infectious readmissions becomes more intuitive: random screening serves to reduce within hospital transmission ($r_0$), whereas on-admission screening serves to reduce the infectious assault from the community population ($1/(1-P)$). Using this

simple mathematical description of transmission it is clear that strategy success is greatly influenced by P.

It must be remembered that all results obtained, both analytical and simulated, are for specific $R_0$, $r_0$ and P values, which may or may not reflect the real situation. In the simulations in Chapters 2 and 3, $r_0 = 1.27$ (taken from work by Cooper *et al.* 2003) and is thought to be similar to the actual value in the UK, although values will vary widely from hospital to hospital and over time. In the analytical results, $r_0 = 0.98$ was used to investigate the situation when $r_0 < 1$ (i.e. insufficient to allow an epidemic in the hospital) and $R_0 > 1$. In this situation readmissions of infected patients are essential for persistence of MRSA within the hospital; implying on-admission screening may be more effective. The analytical results comparing the two strategies do seem to support this theory, but only when P is sufficiently large. When $P>0.495$ it is the reduction in infectious admissions (i.e. $1/(1-P)$) that has the greatest influence on control success and so $R_0$ is reduced further by on-admission screening. Conversely, when P is small it is the reduction of within-hospital transmission that is of greatest benefit, and on-admission screening therefore provides little control. This demonstrates the success of each strategy is inexorably linked to the setting in which it is applied. Therefore when considering how to deal with potential epidemics, such as for VRSA, factors such as estimated reproduction numbers, hospital and community prevalences and readmission rates need to be taken into account. These can only be estimated from surveillance data and the lack of use of such data to inform parameter estimates for transmission is a weakness in these particular results.

**Analysis of real hospital data**

Due to the relationship found between control capability and degree of patient movement in and out of the hospital population, readmissions were explored in more detail in analyses of a real hospital dataset. It was found that on average an infected person had a 44.2% chance of being readmitted to the Trust while still infected. This value is far higher than previous estimates (3.7% (Cooper *et al.*, 2003)) on which the parameters used in the simulation of Chapter 3 were based.

Thus, the model results in Chapter 3 may underestimate the risk of infectious admissions to hospital, and therefore on-admission screening may be of more benefit than predicted.

Analysis of patient admission data found that despite most patients only visiting the hospital a few times, it was the few patients who were frequently readmitted that constituted the majority of admissions (~80%). It is these frequent readmittees, who are most often in hospital and who, as a result, are likely to have most hospital contacts, that make up the 'core group'. Their numerous hospital visits increase their risk of acquiring MRSA, the short time periods over which these readmissions occur mean they have the greatest potential to reintroduce infection and their numerous contacts means they are also the most likely group to transmit infection (especially given the likelihood of high prevalence within the group). However, as these individuals are mostly in contact with each other, there is the potentially advantageous aspect that heterogeneities in readmission create a group who mostly only transmit to each other. Consequently, the dynamics of this 'core group' are important and knowledge of frequent readmittees, for example age/gender rates of admission and discharge, beneficial in that it gives the ability to target control to them. Targeting these groups in infection control measures, by screening on discharge/admission or isolating on admission for example, may serve to reduce the threat they pose.

The fact that individuals are most likely to be readmitted to the hospital from which they were discharged is likely to enhance each of these implications for transmission: the 'core group' has an even greater potential to increase the prevalence within the hospital to which they are specific, but equally their high degree of hospital specificity serves to reduce the threat they pose to other hospitals within the network.

Investigations of a real hospital dataset highlighted demographic information on the patient population potentially of interest in terms of transmission and therefore from an infection control perspective. As may be expected, infants and the elderly

were found to constitute a large proportion of the hospital population, either through large numbers of admissions (infants) or long hospital stays (the elderly). Interestingly, despite relatively short hospital stays, females of child-bearing age were also highlighted as a large constituent of the hospital population. Furthermore, in terms of readmission they were found to have a particularly high chance of being readmitted. Despite potential differences between this demographic group and other patients, such as reduced antibiotic consumption and use of potentially almost self-contained specialties (in terms of staff and patient mixing), young females should perhaps be a future target in infection control.

Given that length of stay is a proven risk factor for HCAI, heterogeneities in patient length of stay may give an indication of those demographic groups who pose a particular infection risk. Generally length of stay increased with age, again implying that the elderly are a particular threat/risk. Moreover, P values associated with older age groups were found to be higher, meaning their probability of infected hospital return is higher than for other groups.

Demographics of the patient population were found to be, to some extent, hospital dependent, with gender, age and specialty distributions varying between hospitals. The demography of individual hospital populations will be a strong influence on the transmission dynamics within that hospital; the patient groups constituting the majority of the hospital population at most times will be those at most risk of acquisition and also those with the greatest transmission potential for that particular hospital.

**Development of a 'real-movements' model**

The development of a mathematical model informed by hospital admission/discharge data allowed real movements in and out of hospital to be incorporated and epidemic behaviour to be simulated in this setting. To the author's knowledge this is the first time such a model has been developed for the purposes of modelling HCAI transmission dynamics. As this model (Chapter 6)

uses data of a sufficient level of detail so as to allow individual-based movements to be simulated, any heterogeneities in patient readmission rates (as described in Chapter 5) are captured. For example, the presence of a 'core group' of readmittees, i.e. patients who are admitted frequently and who actually constitute the majority of the patient population seen in hospital, is incorporated. Despite the increase in average readmission rate and therefore increase in rate of infectious admissions from the community population, the increase in benefit of on-admission screening was not seen to the same degree to that predicted in earlier chapters. However, unlike the results from the model in Chapter 3 (with a lower readmission rate), a strategy in which on-admission screening constituted a small proportion (10%) of the overall screening effort (the remainder made up by random screening) was preferential to an entirely within-hospital based strategy. Therefore the increase in readmission rate increased the benefit in on-admission screening to some degree.

In addition to the development of an IBM using real data to inform patient movement patterns, Chapter 6 also included a further extension to the model in which the Trust's population was modelled in terms of real movements between three individual hospital populations. Previous research has indicated that it is in settings such as this, where a network of hospitals share a community catchment population, that transfer of infectious individuals between hospitals may be sufficient to initiate and sustain endemic behaviour.

The results from the multi-centre model (Chapter 6) showed epidemic/endemic behaviour in each of the hospitals within the network. However, due to heterogeneities in readmission rates coupled with heterogeneities in within hospital reproduction numbers, there was a considerable degree of variability in prevalence achieved at endemic equilibrium between hospitals. The results suggest that infectious readmissions to hospitals may influence the transmission dynamics within an individual hospital more than the within-hospital reproduction number i.e. it is the probability of multiple infectious returns that influences

transmission to a greater extent than the number of secondary infections from a single hospital stay.

As would be expected, epidemic/endemic behaviour observed was dependent on the transmission parameter β. Given this sensitivity to β, the lack of inclusion of any information surrounding heterogeneities in transmission between hospitals/individuals is clearly a limitation in these results. This highlights the need for further investigations into factors that may be of influence to transmission. In addition, the lack of distinction between staff and patients may prevent effects from factors such as long-term carriage by HCW from being captured.

The next step in this research, where real movements of individuals in a multi-centre setting are modelled, would be to incorporate real infection data from this setting and study period. With more time, the value of this research could be increased through working more closely with UHL NHS Trust to obtain this infection data and fitting the 'real-movements' model to it. This would give further insight into the transmission parameters required to most closely simulate the dynamic behaviour seen. This would solve the problems associated with uncertainty regarding the transmission parameter and would highlight model structure deficiencies.

Once realistic (or validated) models of transmission within a multi-centre setting have been established the assessment of control strategies, within this setting, can be explored, thus helping to determine whether the capability of control at one hospital is influenced by that of its neighbours.

Overall, these investigations have furthered previous studies into the transmission dynamics of HCAI as heterogeneity is considered, in terms of both hospital and community populations and the heterogeneous nature of movement between them. The research has demonstrated the potential importance of transmission driven by hospital admissions and has therefore highlighted that consideration of the

community population may be critical to the success of hospital-associated infection control.

**Future Work**

Throughout this research it has been highlighted that surveillance (in this case in the form of screening) is a critical component in any control strategy. In the absence of effective surveillance, infected individuals cannot be detected and control cannot be imposed upon them, meaning the strategy is likely to fail. In all infection control assessments presented, screening is assumed to be both 100% specific and 100% sensitive. This assumption may be justified as reduced effort was put into screening such that a proportion of the population remained unscreened. However, in reality neither specificity nor sensitivity are likely to be 100% accurate and this lack of accuracy has the potential to influence transmission dynamics. A low sensitivity would mean infected patients would go undetected and therefore no control would be imposed on them. Whilst a low specificity would result in susceptible patients being identified as infected and thus 'controlled'. If a component of this control was an IW, for example, the isolation of susceptible individuals would drastically increase their chances of acquiring infection and would also inefficiently use, already limited, resources. Further investigations, using such models as those developed in Chapters 2 and 6 could easily be adapted to discern the change in screening effort, or IW size, required given changes to specificity and sensitivity, or the optimum trade-off between the two for example.

In addition, screening and resulting control is assumed to occur with no time delay. In actuality the turn around time between screening, identifying positives (through culture for example) and imposing control is likely to be at least 24 hours. However, this time period may vary depending on techniques applied, for example for cases that may be considered high risk, faster identification and antibiotic sensitivity tests may be employed. The time delay before control is imposed will clearly have an effect on the transmission dynamics, as it is this interim period in which infected individuals can infect others. Further research

into the extent to which this time delay contributes to epidemic behaviour needs to be undertaken and given the advent of rapid diagnostic screening techniques a theoretical assessment of their potential impact, compared to current techniques, would be of benefit.

The models presented could also be adapted to investigate alternative screening strategies, the obvious next step given the potential importance of infected readmissions, would be targeted screening in which the most frequently admitted patients were given priority. Further to this, with the addition of structuring to the population the assessment of targeting of particular demographic groups could be explored. The degree to which the community/hospital network structure influences control within each hospital may also be crucial to the development of successful control strategies and requires further investigation.

Overall, with relatively few changes to the parameter values, model frameworks or underlying assumptions, different settings, pathogens and control strategies could be investigated.

Of particular value may be the use of such models in the economic assessment of control strategies. As discussed, any intervention carries with it a significant economic burden. If we are to ensure strategy implementation and continued compliance it is important that, at the hospital level, the advantages offset these costs. The incorporation of economic data in the model development would allow cost-effectiveness studies to be carried out. Little work has been undertaken in this area and the allocation of costs to both control methods and their respective benefits is likely to be challenging.

Another area in which further research could be undertaken is in the consideration of CA-MRSA. Despite still being considered as a largely nosocomial problem, MRSA in individuals without recent hospitalization is a rapidly increasing problem. Therefore its inclusion within models such as these, where both hospital and community populations are included explicitly, may provide further insight

into observed patterns. CA-MRSA has been reported to lead to HCAI (O'Brien *et al.*, 1999; Saiman *et al.*, 2003) and so admittees from the community population harbouring these strains have the potential to ignite hospital epidemics. Given the importance of infectious admissions demonstrated in previous chapters, the potential influence of this steadily increasing threat needs to be determined. In a setting of endemicity within the community (maintained without hospital transmission), we could potentially see situations in which any level of hospital-based control will be insufficient due to the relentless infectious assault posed by the community population. A two-strain model, in which both hospital-driven and community-driven dynamics (and interplay between them) are explored, would allow theoretical assessment of control in this, increasingly likely, setting.

# Bibliography

**Abramson, M.A. and Sexton, D.J.** (1999). Nosocomial methicillin-resistant and methicillin-susceptible Staphylococcus aureus primary bacteraemia: at what costs? *Infect Control Hosp Epidemiol.* **20**, 408-411.

**Anderson, R.M. and May, R.M.** (1991). Infectious diseases of humans: dynamics and control. Oxford: Oxford University Press.

**Aucken, H.M., Ganner, M., Murchan, S., Cookson, B.D. and Johnson, A.P.** (2002). A new UK strain of epidemic methicillin-resistant Staphylococcus aureus (EMRSA-17) resistant to multiple antibiotics. *J Antimicrob Chemother.* **50**,171-175.

**Austin, D.J. and Anderson, R.M.** (1999a). Studies of antibiotic resistance within the patient, hospitals and the community using simple mathematical models. *Philos Trans R Soc Lond B Biol Sci.* **354**, 721-738.

**Austin, D.J. and Anderson, R.M.** (1999b). Transmission dynamics of epidemic methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci in England and Wales. *J Infect Dis.* **179**, 883-891.

**Austin, D.J., Bonten, M.J.M., Weinstein, R.A., Slaughter, S. and Anderson R.M.** (1999). Vancomycin-resistant enterococci in intensive-care hospital settings: Transmission dynamics, persistence, and the impact of infection control programs. *Proc Natl Acad Sci USA.* **96**, 6908-6913.

**Austin, D.J., White, N.J. and Anderson R.M.** (1998). The dynamics of drug action on the within-host population growth of infectious agents: melding pharmacokinetics with pathogen population dynamics. *J Theor Biol.* **194**, 313-339.

**Aygen, B., Yoruk, A., Yyldyz, O., Alp, E., Kocagoz, S., Sumerkan, B. and Doganay, M.** (2004). Bloodstream infections caused by *Staphylococcus aureus* in a university hospital in Turkey: clinical and molecular epidemiology of methicillin-resistant *Staphylococcus aureus*. *Clin Microbiol Infect.* **10**, 309-314.

**Ayliffe, G.A.J., Buckles, A., Casewell, M.W., Cookson, B.D., Cox, R.A., Duckworth, G.J., French, G.L., Griffiths-Jones, A., Heathcock, R., Humphreys, H., Keane, C.T., Marples, R.R., Shanson, D.C., Slack, R. and Tebbs, E.** (1998). Revised Methicillin-Resistant Staphylococcus aureus infection control guidelines for hospitals. Report of a combined working party of the British Society for Antimicrobial Chemotherapy, the Hospital Infection Society and the Infection Control Nurses Association, prepared by G. Duckworth, B. Cookson, H. Humphreys and R. Heathcock. *J Hosp Infect*. **39**, 253-290.

**Balaban, N., Goldkorn, T., Nhan, R.T., Dang, L.B., Scott, S., Ridgley, R.M., Rasooly, A., Wright, S.C., Larrick, J.W., Rasooly, R. and Carlson, J.R.** (1998). Autoinducer of virulence as a target for a vaccine and therapy against *Staphylococcus aureus*. *Science*. **280**, 438-440.

**Barber, M. and Rozadowska-Dowzenko, M.** (1948). Infection by penicillin-resistant staphylococci. *Lancet* **ii**, 641.

**Benner, E.J. and Kayser, F.H.** (1968). Growing clinical significance of methicillin-resistance *Staphylococcus aureus*. *Lancet* **ii**, 741-744.

**Bergeron, E., Lavoie, A., Moore, L., Clas, D. and Rossignol, M.** (2005). Comorbidity and age are both independent predictors of length of hospitalization in trauma patients. *Can J Surg*. **48**, 361-366.

**Bhalla, A., Pultz, N.J., Gries, D.M., Ray, A.J., Eckstein, E.C., Aron, D.C. and Donskey, C.J.** (2004). Acquisition of nosocomial pathogens on hands after contact with environmental surfaces near hospitalized patients. *Infect Control Hosp Epidemiol*. **25**, 164-167.

**Blok, H.E., Troelstra, A., Kamp-Hopmans, T.E., Gigengack-Baars, A.C., Vandenbroucke-Grauls, C.M., Weersink, A.J., Verhoef, J. and Mascini, E.M.** (2003). Role of healthcare workers in outbreaks of methicillin-resistant *Staphylococcus aureus*: a 10-year evaluation from a Dutch university hospital. *Infect Control Hosp Epidemiol*. **24**, 679-685.

**Bonhoeffer, S., Lipsitch, M. and Levin B. R.** (1997). Evaluating treatment protocols to prevent antibiotic resistance. *Proc Natl Acad Sci USA*. **94**, 12106-12111.

**Bonten, M.J., Hayden, M.K., Nathan, C., van Voorhis, J., Matushek, M., Slaughter, S., Rice, T. and Weinstein, R.A.** (1996). Epidemiology of colonisation of patients and environment with vancomycin-resistant enterococci. *Lancet*. **348**, 1615-1619.

**Bonten, M.J.M., Austin, D.J. and Lipsitch, M.** (2001). Understanding the Spread of Antibiotic Resistant Pathogens in hospitals: Mathematical Models as Tools for Control. *Clin Infect Dis*. **33**, 1739-1746.

**Borg, M.A.** (2003). Bed occupancy and overcrowding as determinant factors in the incidence of MRSA infections within general ward settings. *J Hosp Infect.* **54**, 316-318.

**Boyce, J.M.** (1992). Methicillin-resistant *Staphylococcus aureus* in hospitals and long-term care facilities: microbiology, epidemiology, and preventive measures. *Infect Control Hosp Epidemiol.* **13**, 725–37.

**Boyce, J.M., Cookson, B., Christiansen, K., Hori, S., Vuopio-Varkila, J., Kocagöz, S., Oztop, A.Y., Vandenbroucke-Grauls, C.M., Harbarth, S. and Pittet, D.** (2005). Meticillin-resistant Staphylococcus aureus. *Lancet Infect Dis.* **5**, 653-663.

**Bradley, S.F., Terpenning, M.S., Ramsey, M.A., Zarins, L.T., Jorgensen, K.A., Sottile, W.S., Schaberg, D.R. and Kauffman, C.A.** (1991). Methicillin-resistant *Staphylococcus aureus :* colonization and infection in a long-term care facility. *Ann Intern Med.* **115**, 417–22.

**Braun, B.I., Kritchevsky, S.B., Wong, E.S., Solomon, S.L., Steele, L., Richards, C.L. and Simmons, B.P., Evaluation of Processes and Indicators in Infection Control Study Group.** (2003). Preventing central venous catheter-associated primary bloodstream infections: characteristics of practices among hospitals participating in the Evaluation of Processes and Indicators in Infection Control (EPIC) study. *Infect Control Hosp Epidemiol.* **24**, 926-935.

**Bukharie, H.A., Abdelhadi, M.S., Saeed, I.A., Rubaish, A.M. and Larbi, E.B.** (2001). Emergence of methicillin-resistant Staphylococcus aureus as a community pathogen. *Diagn Microbiol Infect Dis.* **40**, 1-4.

**Calfee, D.P., Durbin, L.J., Germanson, T.P., Toney, D.M., Smith, E.B. and Farr, B.M.** (2003). Spread of methicillin-resistant *Staphylococcus aureus* (MRSA) among household contacts of individuals with nosocomially acquired MRSA. *Infect Control Hosp Epidemiol.* **24**, 422-426.

**Carbonell, A.M., Lincourt, A.E., Kercher, K.W., Matthews, B.D., Cobb, W.S., Sing, R.F. and Heniford, B.T.** (2005a). Do patient or hospital demographics predict cholecystectomy outcomes? A nationwide study of 93,578 patients. *Surg Endosc.* **19,** 767-773.

**Carbonell, A.M., Lincourt, A.E., Matthews, B.D., Kercher, K.W., Sing, R.F. and Heniford, B.T.** (2005b). National study of the effect of patient and hospital characteristics on bariatric surgery outcomes. *Am Surg.* **71**, 308-314.

**Casewell, M.W.** (1996). New threats to the control of methicillin-resistant *Staphylococcus aureus. J Hosp Infect.* **30**, Suppl, 465-471.

**Chaix, C., Durand-Zaleski, I., Alberti, C. and Brun-Buisson, C.** (1999). Control of endemic methicillin-resistant *Staphylococcus aureus*. A Cost-Benefit Analysis in an Intensive Care Unit. *JAMA*. **282**, 1745-1751.

**CDC** (2002). *Staphylococcus aureus* resistant to vancomycin - United States. *MMWR Morb Mortal Wkly Rep*. **51**, 565-567.

**CDSC** (2002). First report of the Department of Health's mandatory MRSA bacteraemia surveillance scheme in acute NHS Trusts in England: April to September 2001. *Communicable Disease Report Weekly*. **12**(6).

**CDSC** (2004). The third year of regional and national analyses of the Department of Health's mandatory MRSA surveillance scheme in England: April 2001 - March 2004. *Communicable Disease Report Weekly*. **14**(29).

**Coello, R., Glynn, J.R., Gaspar, C., Picazo, J.J. and Fereres, J.** (1997). Risk factors for developing clinical infection with methicillin-resistant *Staphylococcus aureus* (MRSA) amongst hospital patients initially only colonized with MRSA. *J Hosp Infect*. **37**, 39-46.

**Coello, R., Jimenez, J., Garcia, M., Arroyo, P., Minguez, D., Fernandez, C., Cruzet. F. and Gaspar, C.** (1994). Prospective study of infection, colonization and carriage of methicillin-resistant *Staphylococcus aureus* in an outbreak affecting 990 patients. *Eur J Clin Microbiol Infect Dis*. **13**, 74-81.

**Coia, J.E., Duckworth, G.J., Edwards, D.I., Farrington, M., Fry, C., Humphreys, H., Mallaghan, C., Tucker, D.R.; Joint Working Party of the British Society of Antimicrobial Chemotherapy; Hospital Infection Society; Infection Control Nurses Association.** (2006). Guidelines for the control and prevention of meticillin-resistant Staphylococcus aureus (MRSA) in healthcare facilities. *J Hosp Infect*. **63**, Suppl 1, S1-44.

**Cookson, B.** (1997). Controversies: Is it time to stop searching for MRSA? (Screening is still important). *BMJ*. **314**, 664.

**Cookson, B., Peters, B., Webster, M., Phillips, I., Rahman, M. and Noble, W.** (1989). Staff carriage of epidemic methicillin-resistant *Staphylococcus aureus*. *J Clin Microbiol*. **27**, 1471-1476.

**Cooper, B.S., Medley, G.F. and Scott, G. M.** (1999). Preliminary analysis of the transmission dynamics of nosocomial infections: stochastic and management effects. *J Hosp Infect*. **43,** 131–147.

**Cooper, B.S., Medley, G.F., Stone, S.P., Kibbler, C.C., Cookson, B.D., Roberts, J.A., Duckworth, G., Lai, R. and Ebrahim, S.** (2004a). Methicillin-resistant Staphylococcus aureus in hospitals and the community: Stealth dynamics and control catastrophes. *Proc Natl Acad Sci USA*. **101**, 10223-10228.

**Cooper, B.S., Stone, S.P., Kibbler, C.C., Cookson, B.D., Roberts, J.A., Medley, G.F., Duckworth, G.J., Lai, R. and Ebrahim, S.** (2003). Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling. *Health Technol Assess.* **7**(39).

**Cooper, B.S., Stone, S.P., Kibbler, C.C., Cookson, B.D., Roberts, J.A., Medley, G.F., Duckworth, G., Lai, R. and Ebrahim, S.** (2004b). Isolation measures in the hospital management of methicillin resistant Staphylococcus aureus (MRSA): systematic review of the literature. *BMJ.* **329**, 533.

**Cosgrove, S.E., Qi, Y., Kaye, K.S., Harbarth, S., Karchmer, A.W. and Carmeli, Y.** (2005). The impact of methicillin resistance in Staphylococcus aureus bacteremia on patient outcomes: mortality, length of stay, and hospital charges. *Infect Control Hosp Epidemiol.* **26**, 166-174.

**D'Agata, E.M., Horn, M.A. and Webb, G.F.** (2002). The impact of persistent gastrointestinal colonization on the transmission dynamics of vancomycin-resistant enterococci. *J Infect Dis.* **185**, 766-73.

**Dettenkofer, M., Bouletreau, A. and Daschner, F.D.** (1999). Infection control and changes in management of hospitals: the European experience. *J Hosp Infect.* **43**, S161-164.

**Drinka, P.J., Stemper, M.E., Gauerke, C.D., Miller, J.E. and Reed, K.D.** (2004). Screening for Methicillin-Resistant *Staphylococcus aureus* in a nursing home. *Infect Control Hosp Epidemiol.* **25**, 95-96.

**Farr, B.M.** (2004). Prevention and control of methicillin-resistant *Staphylococcus aureus* infections. *Curr Opin Infect Dis.* **17**, 317-322.

**Farrell, A.M., Shanson, D.C., Ross, J.S., Roberts, N.M., Fry, C., Cream, J.J., Staughton, R.C. and Bunker, C.B.** (1998). An outbreak of methicillin-resistant *Staphylococcus aureus* (MRSA) in a dermatology day care unit. *Clin Exp Dermatol.* **23**, 249-253

**Farrington, M., Redpath, C., Trundle, C., Coomber, S. and Brown N.M.** (1998). Winning the battle but losing the war: methicillin-resistant *Staphylococcus aureus* (MRSA) infection at a teaching hospital. *QJM.* **91**, 539-48.

**Fridkin, S.K., Hageman, J.C., Morrison, M., Sanza, L.T., Como-Sabetti, K., Jernigan, J.A., Harriman, K., Harrison, L.H., Lynfield, R., Farley, M.M; Active Bacterial Core Surveillance Program of the Emerging Infections Program Network.** (2005). Methicillin-resistant Staphylococcus aureus disease in three communities. *N Engl J Med.* **352**, 1436-1444.

**Ghani, A.C. and Garnett, G.P.** (2000). Risks of acquiring and transmitting sexually transmitted diseases in sexual partner networks. *Sex Transm Dis.* **27**, 579-87.

**Ghani, A.C., Ison, C.A., Ward, H., Garnett, G.P., Bell, G., Kinghorn, G.R., Weber, J. and Day, S.** (1996). Sexual partner networks in the transmission of sexually transmitted diseases. An analysis of gonorrhea cases in Sheffield, UK. *Sex Transm Dis.* **23**, 498-503.

**Gillet, Y., Issartel, B., Vanhems, P., Fournet, J.C., Lina, G., Bes, M., Vandenesch, F., Piemont, Y., Brousse, N., Floret, D. and Etienne, J.** (2002). Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. *Lancet.* **359**, 753-759.

**Girou, E., Pujade, G., Legrand, P., Cizeau, F. and Brun-Buisson, C.** (1998). Selective screening of carriers for control of methicillin-resistant *Staphylococcus aureus* (MRSA) in high-risk hospital areas with a high level of endemic MRSA. *Clin Infect Dis.* **27**, 543-550.

**Girou, E., Azar, J., Wolkenstein, P., Cizeau, F., Brun-Buisson, C. and Roujeau, J.C.** (2000). Comparison of systematic versus selective screening for methicillin-resistant *Staphylococcus aureus* carriage in a high-risk dermatology ward. *Infect Control Hosp Epidemiol.* **21**, 583-587.

**Glynn, A., Ward, V., Wilson, J., Charlett, A., Cookson, B., Taylor, L. and Cole, N.** (1997). Hospital acquired infection: surveillance, policies and practice. PHLS, London.

**Graffunder, E.M. and Venezia, R.A.** (2002). Risk factors associated with nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection including previous use of antimicrobials. *J Antimicrob Chemother.* **49**, 999-1005.

**Grundmann, H., Hori, S., Winter, B., Tami, A. and Austin, D.J.** (2002). Risk Factors for the Transmission of MRSA in an Adult Intensive Care Unit: Fitting a Model to the Data. *J Infect Dis.* **185**, 481-488.

**Grundmann, H. and Hellriegel, B.** (2006). Mathematical modelling: a tool for hospital infection control. *Lancet Infect Dis.* **6**, 39-45.

**Herold, B.C., Immergluck, L.C., Maranan, M.C., Lauderdale, D.S., Gaskin, R.E., Boyle-Vavra, S., Leitch, C.D. and Daum, R.S.** (1998). Community-acquired methicillin-resistant Staphylococcus aureus in children with no identified predisposing risk. *JAMA.* **279**, 593-598.

**Hiramatsu, K., Hanaki, H. and Ino, T.** (1997). Methicillin resistance *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility *J Antimicrob Chemother.* **40**, 135-136.

**Hota, B.** (2004). Contamination, disinfection and cross-colonization: are hospital surfaces reservoirs for nosocomial infection? *Clin Infect Dis.* **39**, 1182-1189.

**Howe, R.A., Bowker, K.E., Walsh, T.R., Feest, T.G. and MacGowan, A.P.** (1998). Vancomycin resistant *Staphylococcus aureus. Lancet.* **351**, 602.

**Huges, D. and Anderson, D.I.** (2001). Antibiotic Development and Resistance. Taylor and Francis, London, NY.

**Jernigan, J.A., Clemence, M.A., Stott, G.A., Titus, M.G., Alexander, C.H., Palumbo, C.M. and Farr, B.M.** (1995). Control of methicillin-resistant Staphylococcus aureus at a university hospital: one decade later. *Infect Control Hosp Epidemiol.* **16**, 686-96.

**Jernigan, J.A., Titus, M.G., Groschel, D.H., Getchell-White, S. and Farr, B.M.** (1996). Effectiveness of contact isolation during a hospital outbreak of methicillin-resistant Staphylococcus aureus. *Am J Epidemiol.* **143**, 496-504.

**King, M.D., Humphrey, B.J., Wang, Y.F., Kourbatova, E.V., Ray, S.M. and Blumberg, H.M.** (2006). Emergence of community-acquired methicillin-resistant *Staphylococcus aureus* USA 300 clone as the predominant cause of skin and soft-tissue infections. *Ann Intern Med.* **144**, 309-317.

**Kluytmans, J., Van Belkum, A. and Verbrugh, H.** (1997). Nasal carriage of *Staphylococcus aureus*: epidemiology, underlying mechanisms, and associated risks. *Clinical Microbiol Rev.* **10**, 505-20

**Kunori, T., Cookson, B., Roberts, J.A., Stone, S. and Kibbler, C.** (2002). Cost-effectiveness of different MRSA screening methods. *J Hosp Infect.* **51**, 189-200.

**Lauria, F.N. and Angeletti, C.** (2003). The impact of nosocomial infections on hospital care costs. *Infection.* **31,** Suppl 2, 35-43.

**Leman, R., Alvardo-Ramy, F., Pocock, S., Barg, N., Kellum, M., McAllister, S., Cheek, J. and Kuehnert, M.** (2004). Nasal carriage of methicillin-resistant Staphylococcus aureus in an American Indian population. *Infect Control Hosp Epidemiol.* **25**, 121-125.

**Lepelletier, D., Perron, S., Huguenin, H., Picard, M., Bemer, P., Caillon, J., Juvin, M.E. and Drugeon, H.B.** (2004). Which strategies follow from the surveillance of multidrug-resistant bacteria to strengthen control of their spread? A French experience. *Infect Control Hosp Epidemiol.* **25**, 162-164.

**Levin, B.R.** (2001). Minimizing Potential Resistance: A Population Dynamics View. *Clin Infect Dis.* **33**, Suppl 3. S161-169.

**Levin, S.A. and Andreasen, V.** (1999). Disease transmission dynamics and the evolution of antibiotic resistance in hospitals and communal settings. *Proc Natl Acad Sci USA*. **96**, 800-801.

**Levin, B.R., Lipsitch, M. and Bonhoeffer, S.** (1999). Population Biology, Evolution, and Infectious Disease: Convergence and Synthesis. *Science*. **283**, 806.

**Levin B.R., Lipsitch M., Perrot V., Schrag S., Antia R., Simonsen L., Walker, N.M., and Stewart F.M.** (1997). The population genetics of antibiotic resitance. *Clin Infect Dis*. **24**, Suppl 1, S9-16

**Lipsitch, M., Bergstrom, C.T. and Levin, B.R.** (2000). The epidemiology of antibiotic resistance in hospitals: paradoxes and prescriptions. *Proc Natl Acad Sci USA*. **97**, 1938-1943.

**Loulergue, J., de Gialluly, C., Morange, V., Holstein, A., van der Mee-Marquet, N. and Quentin, R.** (2006). Evaluation of a new chromogenic medium for isolation and presumptive identification of methicillin-resistant Staphylococcus aureus from human clinical specimens. *Eur J Clin Microbiol Infect Dis*. **25**, 407-409.

**Lowy, F.D.** (1998). Review article: Staphylococcus aureus infections. *N Engl J Med*. **339**, 520-532.

**Marshall, A., Vasilakis, C. and El-Dorzi, E.** (2005). Length of stay based patient flow models: recent developments and future directions. *Health Care Manag Sci*. **8**, 213-220.

**Massad, E., Lundberg, S. and Yang, H.M.** (1993). Modeling and simulating the evolution of resistance against antibiotics. *Int J Biomed Comput*. **33**, 65-81.

**Mehtar, S.** (1995). Infection control programmes - are they cost effective? *J Hosp Infect*. **30**, S, 26-34

**Metan, G., Zarakolu, P. and Unal, S.** (2005). Rapid detection of antibacterial resistance in emerging Gram-positive cocci. *J Hosp Infect*. **61**, 93-99.

**Mulligan, M.E., Murray-Leisure, K.A., Ribner, B.S., Standiford, H.C., John, J.F., Korvick, J.A., Kauffman, C.A. and Yu, V.L.** (1993). Methicillin-resistant Staphylococcus aureus: a consensus review of the microbiology, pathogenesis. and epidemiology with implications for prevention and management. *Am J Med*. **94**,313-328.

**Moellering, R.C. Jr.** (2006). The growing menace of community-acquired methicillin-resistant Staphylococcus aureus. *Ann Intern Med*. **144**. 368-370.

**Naimi, T.S., LeDell, K.H., Como-Sabetti, K., Borchardt, S.M., Boxrud, D.J., Etienne, J., Johnson, S.K., Vandenesch, F., Fridkin, S., O'Boyle, C., Danila,**

**R.N. and Lynfield, R.** (2003). Comparison of community and health care-associated methicillin-resistant *Staphylococcus aureus* infection. *JAMA.* **290**, 2976-2984.

**Neu, H.C.** (1992). The crisis in antibiotic resistance. *Science.* **257**, 1064-1073.

**Nijssen, S., Bonten, M.J., Franklin, C., Verhoef, J., Hoepelman, A.I.M. and Weinstein, R.A.** (2003). Relative risk of physicians and nurses to transmit pathogens in a medical intensive care unit. *Arch Intern Med.* **163**, 2785-2786.

**North, E.A.** (1946). Acquired resistance of staphylococci to the action of penicillin. *Med J Aust.* **1**, 176-179.

**O'Brien, F.G., Pearman, J.W., Gracey, M., Riley, T.V. and Grubb, W.B.** (1999). Community strain of MRSA involved in a hospital outbreak. *J. Clin. Microbiol.* **37**, 2858-2862.

**Papia, G., Louie, M., Tralla, A., Johnson, C., Collins, V. and Simor, A.E.** (1999). Screening high-risk patients for methicillin-resistant *Staphylococcus aureus* on admission to the hospital: is it cost effective? *Infect Control Hosp Epidemiol.* **20**, 473-477.

**Pate, K.R., Nolan, R.L., Bannerman, T.L. and Feldman, S.** (1995). Methicillin-resistant Staphylococcus aureus in the community. *Lancet.* **346**, 978

**Peacock, J.E., Marsik, F.J. and Wenzel, R.P.** (1980). Methicillin resistant *Staphylococcus aureus*: introduction and spread within a hospital. *Ann Intern Med.* **93,** 526-532.

**Pelupessy, I., Bonten, J.M. and Diekmann, O.** (2002). How to assess the relative importance of different colonisation routes of pathogens within hospital settings. *Proc Natl Acad Sci USA.* **99**, 5601-5605.

**Pittet, D.** (2000). Improving compliance with hand hygiene in hospitals. *Infect Control Hosp Epidemiol.* **21**, 381-386.

**Pittet, D., Allegranzi, B., Sax, H., Dharan, S., Pessoa-Silva, C.L., Donaldson, L., Boyce, J.M.; WHO Global Patient Safety Challenge, World Alliance for Patient Safety.** (2006). Evidence-based model for hand transmission during patient care and the role of improved practices. *Lancet Infect Dis.* **6**, 641-52.

**Pittet, D., Safran, E., Harbarth, S., Borst, F., Copin, P., Rohner, P., Scherrer, J.R. and Auckenthaler, R.** (1996). Automatic alerts for methicillin-resistant Staphylococcus aureus surveillance and control: role of a hospital information system. *Infect Control Hosp Epidemiol.* **17**, 496-502.

**Pittet, D. and Waldvogel, F.A.** (1997). To control or not to control colonization with MRSA ... that's the question! *QJM.* **90**, 239-241.

**Rahman, M,, Sanderson, P.J., Bentley, A.H., Barrett, S.P., Karim, Q.N., Teare, E.L., Chaudhuri, A., Alcock, S.R., Corcoran, G.D., Azadian, B., Dance, D.A., Gaunt, P.N., Cunningham, R., Ahmad, F.J., Garvey, R.J., Chattopadhyay, B., Wiggins, R.J., Sheppard, M., Wright, E.P., Moulsdale, M. and Falkiner, F.** (2000). Control of MRSA. *J Hosp Infect.* **44**, 151-153.

**Robotham, J.V., Jenkins, D.R. and Medley, G.F.** (2007a). Screening Strategies in Surveillance and Control of Methicillin-Resistant *Staphylococcus aureus* (MRSA). *Epidemiol Infect.* **135**, 328-342.

**Robotham, J.V., Scarff, C.A., Jenkins, D.R. and Medley, G.F.** (2007b). Methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitals and the community: model predictions based on the UK situation. *J Hosp Infect.* **65**, Suppl 2, 93-99.

**Safdar, N. and Maki, D.G.** (2002). The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant Staphylococcus aureus, enterococcus, gram-negative bacilli, Clostridium difficile, and Candida. *Ann Intern Med.* **136**, 834-44.

**Saiman, L., O'Keefe, M., Graham, P.L. 3rd, Wu, F., Said-Salim, B., Kreiswirth, B., LaSala, A., Schlievert, P.M. and Della-Latta, P.** (2003). Hospital transmission of community-acquired methicillin-resistant Staphylococcus aureus among postpartum women. *Clin Infect Dis.* **37**, 1313-1319.

**Salgado, C.D. and Farr B.M.** (2003). MRSA and VRE: Preventing Patient-to-Patient Spread. *Infect Med.* **20**, 194-200.

**Salgado, C.D., Farr, B.M. and Calfee, D.P.** (2003). Community-acquired methicillin-resistant *Staphylococcus aureus*: a meta-analysis of prevalence and risk factors. *Clin Infect Dis.* **36**, 131-139.

**Salmenlinna, S., Lyytikainen, O. and Vuopio-Varkila, J.** (2002). Community-acquired methicillin-resistant Staphylococcus aureus, Finland. *Emerg Infect Dis.* **8**, 602-607.

**Sanchez, V., Vazquez, J.A., Barth-Jones, D., Dembry, L., Sobel, J.D. and Zevros, M.J.** (1992). Epidemiology of nosocomial acquisition of *Candida lusitaniae*. *J Clin Micribiol.* **30**, 3005-3008.

**Scanvic, A., Denic, L., Gaillon, S., Giry, P., Andremont, A. and Lucet, J.C.** (2001). Duration of colonization by methicillin-resistant *Staphylococcus aureus* after hospital discharge and risk factors for prolonged carriage. *Clin Infect Dis.* **32**, 1393-1398.

**Sébille, V., Chevret, S. and Valleron, A.J.** (1997). Modeling the spread of resistant nosocomial pathogens in an intensive-care unit. *Infect Control Hosp Epidemiol.* **18**, 84-92.

**Sébille, V. and Valleron, A.J.** (1997). A Computer Simulation Model for the Spread of Nosocomial Infections Caused by Multidrug-Resistant Pathogens. *Comput Biomed Res.* **30**, 307-322.

**Sherertz, R.J., Reagan, D.R., Hampton, K.D., Robertson, K.L., Streed, K.A., Hoen, H.M., Thomas, R. and Gwaltney, J.M.** (1996). A cloud adult: The Staphylococcus aureus – virus interaction revisited. *Ann Intern Med.* **124**, 539-547.

**Smith, D.L., Dushoff, J., Perencevich, E.N., Harris, A.D. and Levin, S.A.** (2004). Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: Resistance is a regional problem. *Proc Natl Acad Sci USA.* **101**, 3709-3714.

**Smith, D.L., Levin, S.A. and Laxminarayan, R.** (2005). Strategic interactions in multi-institutional epidemics of antibiotic resistance. *Proc Natl Acad Sci USA.* **102**, 3153-3158.

**Starr, J.** (2005). Clostridium difficile associated diarrhoea: diagnosis and treatment.
*BMJ.* **331**, 498-501.

**Stewart, F.M., Antia, R., Levin, B.M., Lipsitch, M. and Mittler, J.E.** (1998). The Population Genetics of Antibiotic Resistance II: Analytic Theory for Sustained Populations of Bacteria in a Community of Hosts. *Theor Popul Biol.* **53**, 152-165.

**Stefani, S. and Varaldo, P.E.** (2003). Epidemiology of methicillin-resistant staphylococci in Europe. *Clin Microbiol Infect.* **9**, 1179-1186.

**Sulakvelidze, A. and Morris, J.G. Jr.** (2001). Bacteriophages as therapeutic agents. *Ann Med.* **33**, 507-509.

**Sutton, A.J., Gay, N.J., Edmunds, W.J., Andrews, N.J., Hope, V.D., Gilbert, R.L., Piper, M. and Gill, O.N.** (2006). Modelling the hepatitis B vaccination programme in prisons. *Epidemiol Infect.* **134**, 231-242.

**Swartz, M.N.** (1994). Hospital-acquired infections: diseases with increasingly limited therapies. *Proc Natl Acad Sci USA.* **91**, 2420-2427.

**Tenover, F.C**. (2007). Rapid detection and identification of bacterial path*ogens using novel molecular technologies: infection control and beyond. Clin Infect Dis.* **44**, 418-423.

**Tenover, F.C. and McGowen J.E. Jr.** (1996). Reasons for the emergence of antibiotic resistance. *Am J Med Sci.* **311,** 9-16.

**Thompson, R.L., Cabezudo, I. and Wenzel, R.P.** (1982). Epidemiology of nosocomial infections caused by methicillin-resistant Staphylococcus aureus. *Ann Intern Med.* **97**, 309-317.

**Tomic, V., Svetina Sorli, P., Trinkaus, D., Sorli, J., Widmer, A.F. and Trampuz, A.** (2004). Comprehensive strategy to prevent nosocomial spread of methicillin-resistant Staphylococcus aureus in a highly endemic setting. *Arch Intern Med.* **164**, 2038-2043.

**Tsiodras, S., Gold, H.S., Sakoulas, G., Eliopoulos, G.M., Wennersten, C., Venkataraman, L., Moellering, R.C. and Ferraro, M.J.** (2001). Linezolid resistance in a clinical isolate of *Staphylococcus aureus. Lancet.* **358**, 207-208.

**van den Broek, P.J.** (2003). [Staphylococcus aureus, a successful pathogen]. *Ned Tijdschr Geneeskd* **147**, 1045-1048.

**van Saene, H.K.F., Weir, W.I., de la Cal, M.A., Silvestri, L., Petros, A.J. and Barrett, S.** (2004). MRSA--time for a more pragmatic approach? *J Hosp Infect.* **56**, 170-174.

**Vegni, F.E., Panceri, M.L., Biffi, M., Banfi, E., Porretta, A.D. and Privitera, G.** (2004). Three scenarios of clinical claim reimbursement for nosocomial infection: the good, the bad, and the ugly. *J Hosp Infect.* **56**, 150-155.

**Wannet, W.J., Spalburg, E., Heck, M.E., Pluister, G.N., Tiemersma, E., Willems, R.J., Huijsdens, X.W., de Neeling, A.J. and Etienne, J.** (2005). Emergence of virulent methicillin-resistant Staphylococcus aureus strains carrying Panton-Valentine leucocidin genes in The Netherlands. *J Clin Microbiol.* **43**, 3341-3345.

**Westran, J.K. and Struthers, R.P.** (2003). Clinical Bacteriology. Manson Publishing Ltd., London.

**Wernitz, M.H., Swidsinki, S., Weist, K., Sohr, D., Witte, W., Franke, K-P., Roloff, D., Rüden, H. and Veit, S.K**. (2005). Effectiveness of a hospital-wide selective screening programme for methicillin-resistant *Staphylococcus* aureus (MRSA) carriers at hospital admission to prevent hospital-acquired MRSA infections. *Clin Microbiol Infect.* **11**, 457-465.

**Wu, S., Piscitelli, C., de Lencastre, H. and Tomas, A.** (1996). Tracking the evolutionary origin of the methicillin resistance gene: cloning and sequencing of a homologue of mecA from a methicillin susceptible strain of Staphylococcus sciuri. *Microb Drug Resist.* **2**, 435-441.

# Appendix 1

| | Leicester Royal Infirmary | | Leicester General Hospital | | Glenfield General Hospital | |
|---|---|---|---|---|---|---|
| | In- and outpatients | Inpatients only | In- and outpatients | Inpatients only | In- and outpatients | Inpatients only |
| N | 360127 | 825499 | 202486 | 376320 | 116895 | 199533 |
| Mean | 39.26 | 39.86 | 49.55 | 48.95 | 61.10 | 59.32 |
| Median | 35 | 36 | 53 | 50 | 66 | 62 |
| Mode | 0 | 0 | 0 | 0 | 74 | 74 |
| Range | 0-107 | 0-107 | 0-109 | 0-109 | 0-106 | 0-106 |
| IQR | 14, 35, 66 | 20,36,63 | 29, 53, 73 | 30,50,70 | 51, 66, 76 | 48,62,74 |

**Table A1.1** Summary statistics for age by hospital.

| | | Discharge Hospital | | | | | |
|---|---|---|---|---|---|---|---|
| | | GH | | LGH | | LRI | |
| | | Freq | % | Freq | % | Freq | % |
| **Admitting Hospital** | GH | 198926 | 0.9970 | 283 | 0.0014 | 325 | 0.0016 |
| | LGH | 411 | 0.0011 | 375530 | 0.9978 | 400 | 0.0011 |
| | LRI | 1086 | 0.0013 | 1060 | 0.0013 | 823450 | 0.9974 |

**Table A1.2** Transfers between hospitals, including in- and outpatients, n = 1401471.

| | | Discharge Hospital | | | | | |
|---|---|---|---|---|---|---|---|
| | | GH | | LGH | | LRI | |
| | | Freq | % | Freq | % | Freq | % |
| **Admitting Hospital** | GH | 116291 | 0.9948 | 283 | 0.0024 | 322 | 0.0028 |
| | LGH | 410 | 0.0020 | 201695 | 0.9960 | 398 | 0.0020 |
| | LRI | 1064 | 0.0030 | 1049 | 0.0029 | 358076 | 0.9941 |

**Table A1.3** Transfers between hospitals, including inpatients only, n = 679588.

| | Female | | Male | |
|---|---|---|---|---|
| | **In- and outpatients** | **Inpatients only** | **In- and outpatients** | **Inpatients only** |
| N | 810434 | 377435 | 591027 | 302153 |
| Mean | 3.08 | 6.61 | 3.43 | 6.7 |
| Median | 0 | 3 | 1 | 3 |
| Mode | 0 | 1 | 0 | 1 |
| Range | 0-1398 | 1-1398 | 0-1446 | 1-1446 |
| IQR | 0,2 | 1,7 | 1,3 | 1,7 |

**Table A1.4** Summary statistics for length of stay by gender.

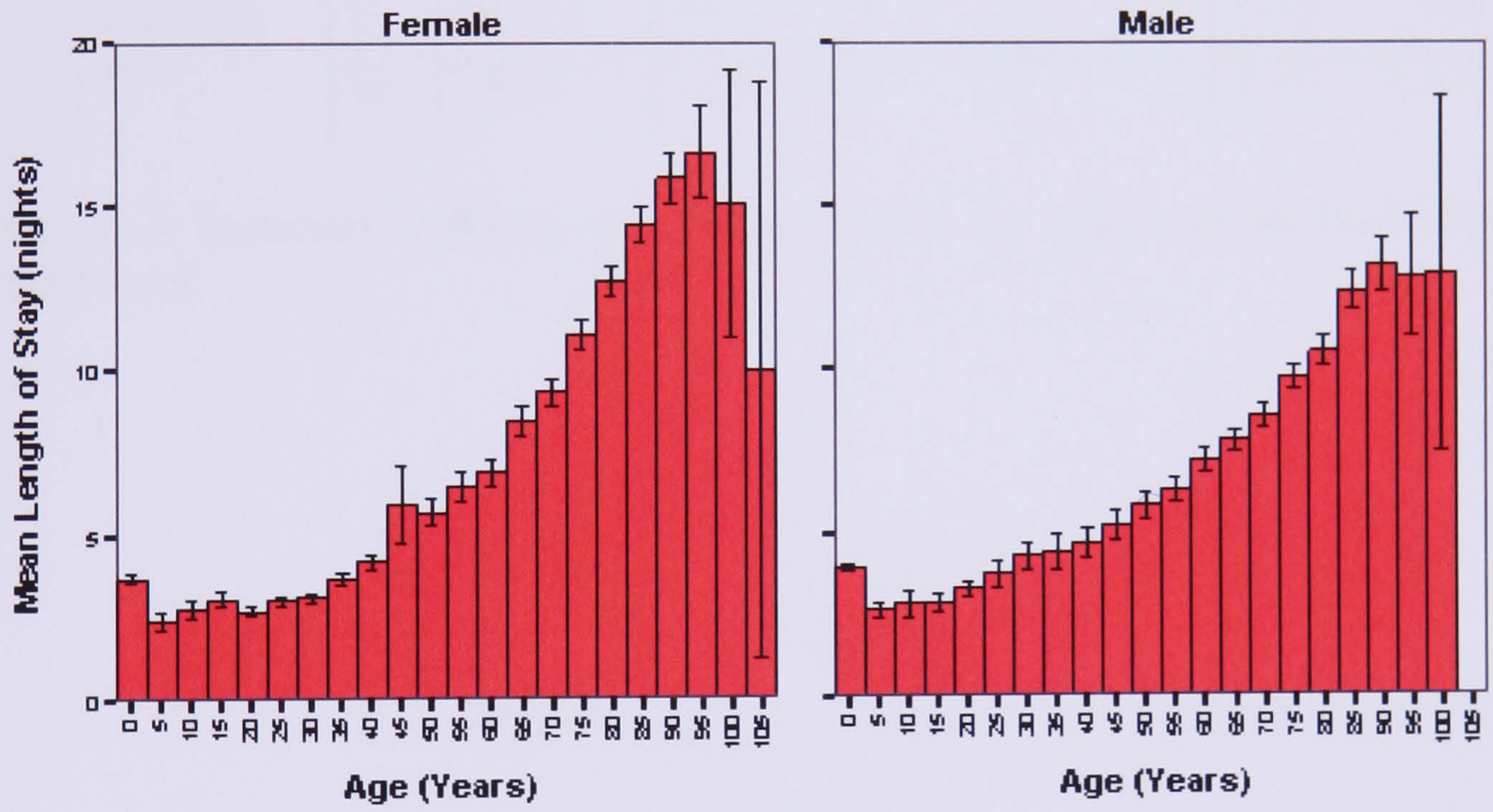



**Figure A1.1** Mean length of stay by age, split by gender. Includes inpatients only, for females n= 377406, for males n= 302102.

| | | | N | Mean | Median | Mode | Range | IQR |
|---|---|---|---|---|---|---|---|---|
| **Leicester Royal Infirmary** | In- and outpatients | F | 498216 | 2.39 | 0 | 0 | 0-1398 | 0.2 |
| | | M | 327372 | 2.69 | 0 | 0 | 0-1446 | 0.2 |
| | Inpatients only | F | 203807 | 5.85 | 2 | 1 | 1-1398 | 1.5 |
| | | M | 156382 | 5.63 | 2 | 1 | 1-1446 | 1.5 |
| **Leicester General Hospital** | In- and outpatients | F | 216481 | 3.66 | 1 | 0 | 0-453 | 0.3 |
| | | M | 159858 | 4.11 | 1 | 0 | 0-428 | 0.4 |
| | Inpatients only | F | 115471 | 6.86 | 3 | 1 | 1-453 | 1.7 |
| | | M | 87032 | 7.75 | 3 | 1 | 1-428 | 1.8 |
| **Glenfield General Hospital** | In- and outpatients | F | 95737 | 5.36 | 1 | 0 | 0-269 | 0.7 |
| | | M | 103797 | 4.69 | 1 | 0 | 0-367 | 0.6 |
| | Inpatients only | F | 58157 | 8.82 | 5 | 1 | 1-269 | 2,10 |
| | | M | 58739 | 8.29 | 5 | 1 | 1-137 | 2,10 |

**Table A1.5** Summary statistics for length of stay by gender at an individual hospital level.

# Appendix 2

| $\mathbf{R_{ij}}$ | $\mathbf{Q_{ij}}$ |
|---|---|
| $R_{11} = r_{0_1}\left(\frac{1}{1-Q_{11}}\right)$ | $Q_{11} = P_{11} + P_{12}Q_{21} + P_{13}Q_{31}$ |
| $R_{22} = r_{0_2}\left(\frac{1}{1-Q_{22}}\right)$ | $Q_{22} = P_{22} + P_{21}Q_{12} + P_{23}Q_{32}$ |
| $R_{33} = r_{0_3}\left(\frac{1}{1-Q_{33}}\right)$ | $Q_{33} = P_{33} + P_{31}Q_{13} + P_{32}Q_{23}$ |
| $R_{21} = \frac{\left(P_{21} + P_{23}P_{31}\right)}{1-P_{32}P_{23}}R_{11}$ | $Q_{21} = \frac{\left(P_{21} + P_{23}P_{31}\right)}{1-P_{32}P_{23}}$ |
| $R_{31} = \frac{\left(P_{31} + P_{32}P_{21}\right)}{1-P_{32}P_{23}}R_{11}$ | $Q_{31} = \frac{\left(P_{31} + P_{32}P_{21}\right)}{1-P_{32}P_{23}}$ |
| $R_{12} = \frac{\left(P_{12} + P_{13}P_{32}\right)}{1-P_{13}P_{31}}R_{22}$ | $Q_{12} = \frac{\left(P_{12} + P_{13}P_{32}\right)}{1-P_{13}P_{31}}$ |
| $R_{32} = \frac{\left(P_{32} + P_{31}P_{12}\right)}{1-P_{31}P_{13}}R_{22}$ | $Q_{32} = \frac{\left(P_{32} + P_{31}P_{12}\right)}{1-P_{31}P_{13}}$ |
| $R_{13} = \frac{\left(P_{13} + P_{12}P_{23}\right)}{1-P_{12}P_{21}}R_{33}$ | $Q_{13} = \frac{\left(P_{13} + P_{12}P_{23}\right)}{1-P_{12}P_{21}}$ |
| $R_{23} = \frac{\left(P_{23} + P_{21}P_{13}\right)}{1-P_{21}P_{12}}R_{33}$ | $Q_{23} = \frac{\left(P_{23} + P_{21}P_{13}\right)}{1-P_{21}P_{12}}$ |

**Table A2.1** Full equations for $R_{ij}$ and $Q_{ij}$, in terms of $P_{ij}$ and $r_{0i}$ where i = hospital number (i.e. hospital 1 , 2 or 3).